Official Title:	A Safety and Efficacy Study of Ruxolitinib Cream Combined With Narrow-Band Ultraviolet B Phototherapy in Participants With Vitiligo
NCT Number:	NCT05247489
Document Date:	Clinical Study Protocol Original Version: 30 September 2021

Clinical Study Protocol

INCB 18424-217

A Safety and Efficacy Study of Ruxolitinib Cream Combined With Narrow-Band Ultraviolet B Phototherapy in Participants With Vitiligo

Product:	**Ruxolitinib Cream**
IND Number:	**77,101**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, Delaware, USA 19803**
Original Protocol:	**30 SEP 2021**

INVESTIGATOR'S AGREEMENT

I have read the INCB 18424-217 Protocol (dated 30 SEP 2021) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

_____

(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

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LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
AA	alopecia areata
AD	atopic dermatitis
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice daily
BMI	body mass index
BSA	body surface area
CFR	Code of Federal Regulations
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
EOT	end of treatment
F-BSA	facial body surface area
[redacted]	[redacted]
[redacted]	[redacted]
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
F-VASI	Face Vitiligo Area Scoring Index
F-VASI25/50/75/90	≥ 25%/ 50%/ 75%/ 90% improvement from baseline in Face Vitiligo Area Scoring Index score
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	identification
IEC	independent ethics committee
IRB	institutional review board

Abbreviations and Special Terms	Definition
IRT	interactive response technology
JAK	Janus kinase
MedDRA	Medical Dictionary for Regulatory Activities
NB-UVB	narrow-band ultraviolet B
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PK	pharmacokinetic
PUVA	psoralen and ultraviolet A
QD	once daily
RSI	reference safety information
SAE	serious adverse event
SD	standard deviation
SoA	schedule of assessments
SOP	standard operating procedure
SPF	sun protection factor
SUSAR	suspected unexpected adverse reaction
T-BSA	total body surface area
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
T-PaGVA	total body assessment of Patient's Global Vitiligo Assessment
[redacted]	[redacted]
TSH	thyroid-stimulating hormone
T-VASI	total body Vitiligo Area Scoring Index
T-VASI25/50/75/90	≥ 25%/ 50%/ 75%/ 90% improvement in total body Vitiligo Area Scoring Index
TYK	tyrosine kinase
ULN	upper limit of normal
UV	ultraviolet
VASI	Vitiligo Area Scoring Index
[redacted]	[redacted]
[redacted]	[redacted]
WHO	World Health Organization
[redacted]	[redacted]
WOCBP	women of childbearing potential

1. PROTOCOL SUMMARY

Protocol Title:

A Safety and Efficacy Study of Ruxolitinib Cream Combined With Narrow-Band Ultraviolet B Phototherapy in Participants With Vitiligo

Protocol Number: INCB 18424-217

Objectives and Endpoints:

Table 1 presents the primary objective and endpoint.

Table 1: Primary Objective and Endpoint

Objective	Endpoint
Primary	
To evaluate the efficacy of ruxolitinib cream in combination with NB-UVB in participants with vitiligo.	Change from baseline in T-VASI at Week 48.

Overall Design:

Table 2 presents the key study design elements. Further study details are presented after the table.

Table 2: Key Study Design Elements

Study Phase	Phase 2
Clinical Indication	Patients with nonsegmental vitiligo
Population	Males and female participants, aged ≥ 12 years, who have vitiligo with ≥ 0.5 F-VASI, ≥ 3.0 T-VASI (body areas not including the face), and total body vitiligo area (facial and nonfacial) not exceeding 10% BSA.
Number of Participants	Approximately 50 participants will receive ruxolitinib 1.5% cream BID
Study Design	Open-label
Estimated Duration of Study Participation	Screening: Up to 30 days Treatment period: 48 weeks Safety follow-up: 30 days after last application of study drug or last study visit Total: Up to approximately 56 weeks
DSMB/DMC	No
Coordinating Principal Investigator	[redacted]

Treatment Groups and Duration:

This is an open-label study in which participants will apply ruxolitinib 1.5% cream BID to all depigmented areas up to 10% BSA for up to 48 weeks. Participants should continue to treat depigmented areas identified for treatment at baseline regardless of whether the area begins to improve or fully repigment.

On Day 1, all participants will apply ruxolitinib 1.5% cream BID as monotherapy. At Week 12, participants will apply ruxolitinib 1.5% cream alone or in combination with NB-UVB based on improvement in T-VASI score. Participants who have < T-VASI25 will have NB-UVB phototherapy added to their ruxolitinib 1.5% cream BID regimen (Group A). NB-UVB will be given 3 times per week through Week 48 (36 weeks). Participants who have ≥ T-VASI25 at Week 12 will continue on ruxolitinib 1.5% cream BID alone (Group B). For participants who receive combination therapy, NB-UVB machines will be supplied by the sponsor for at home use during the study.

Figure 1 presents the study design schema. Table 3 presents the schedule of activities for the monotherapy portion of the study (screening through Week 12). Table 4 presents the schedule of activities for Week 16 through the end of the study.

Figure 1: Study Design Schema

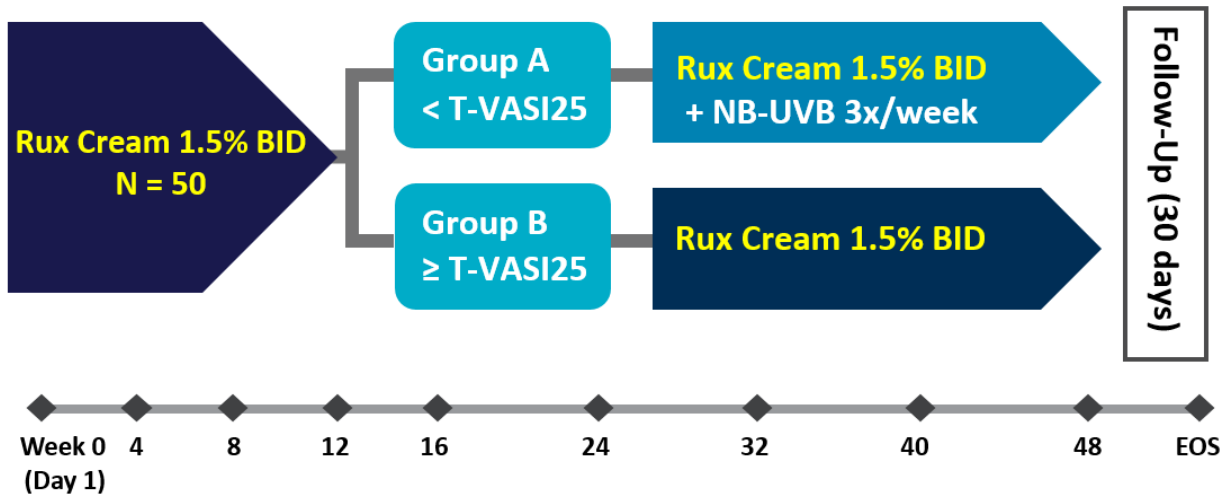

Table 3: Schedule of Assessments for Screening Through Week 12

Procedure	Screening	Treatment Run-In				Notes
	Days −30 to −1	Day 1	Week 4 (± 3 d)	Week 8 (± 3 d)	Week 12 (± 3 d)	
Administrative procedures						
Informed consent	X					Section 8.1.1
Contact IRT	X	X	X	X	X	Section 8.1.3
Inclusion and exclusion criteria	X	X				Section 5
Demography	X					Section 8.1.5.1
General and vitiligo medical history	X					Section 8.1.5.2
Prior/concomitant medications	X	X	X	X	X	Section 6.6
Apply study cream		X	X	X	X	Should be applied by the participant under direct supervision of the site staff. Study cream should be applied after PK or translational blood draws on applicable days.
Dispense (D) and return (R) study cream and reminder/diary cards		D	R/D	R/D	R/D	All tubes of study drug to be weighed before dispensing and when returned. Tubes may not be redispensed.
Collect study cream tubes and collect/review study cream diary cards			X	X	X	
Assess compliance of study cream			X	X	X	Compliance is based on the number of applications. Section 6.4.
Safety assessments						
AE assessment*	X	X	X	X	X	*If an AE is noted, relevant body systems should be physically examined in a targeted physical exam. Section 8.3.2 Ad hoc photography of skin-related AEs should occur as applicable. Section 8.2.5
Comprehensive physical examination	X				X	Section 8.3.2
Vital signs	X	X	X	X	X	Section 8.3.3
12-lead ECG	X					12-lead ECG performed within 2 months before baseline is acceptable. Section 8.3.4

Table 3: Schedule of Assessments for Screening Through Week 12 (Continued)

Procedure	Screening	Treatment Run-In				Notes
	Days −30 to −1	Day 1	Week 4 (± 3 d)	Week 8 (± 3 d)	Week 12 (± 3 d)	
Efficacy assessments						
F-BSA	X	X	X	X	X	Section 8.2.1
T-BSA	X	X	X	X	X	Includes facial and nonfacial areas. Section 8.2.1
F-VASI	X	X	X	X	X	Section 8.2.2
T-VASI	X	X	X	X	X	Includes facial and nonfacial areas. Section 8.2.2
[redacted]						
Photography of face	X	X*			X	*If photo quality at screening is not adequate, the photography may be repeated on Day 1. Section 8.2.5
Photography of nonfacial target area	X	X*			X	
[redacted]						
Laboratory assessments						
Hematology and chemistry assessments	X	X			X	Section 8.3.5
Serology and thyroid testing	X					Section 8.3.5.2
Urinalysis	X					Section 8.3.5
FSH	X					
Pregnancy testing (serum)	X					Section 8.3.5.1
Pregnancy testing (urine)		X	X	X	X	Section 8.3.5.1

Table 3: Schedule of Assessments for Screening Through Week 12 (Continued)

Procedure	Screening	Treatment Run-In				Notes
	Days −30 to −1	Day 1	Week 4 (± 3 d)	Week 8 (± 3 d)	Week 12 (± 3 d)	
PK and translational assessments						
PK blood draw			X		X	Blood samples must not be drawn from the area that has been treated with study cream. Samples will be drawn at preapplication. Section 8.4
[redacted]						
Vitamin D assessment	X	X			X	
[redacted]						

Note: Unscheduled visits may occur at any time at the investigator's discretion, and appropriate clinical and laboratory tests may be performed, as clinically indicated.

Table 4: Schedule of Assessments Week 16 Through End of Study

Procedure	Week 16 (± 3 d)	Week 24 (± 7 d)	Week 32 (± 7 d)	Week 40 (± 7 d)	Week 48 (EOT) (± 7 d)	Safety Follow-Up 30 days (EOT*+7 d) (EOS)	Notes *After last application of study cream or last visit.
Administrative procedures							
Contact IRT	X	X	X	X	X	X	Section 8.1.3
Prior/concomitant medications	X	X	X	X	X	X	Section 6.6
Apply study cream	X	X	X	X			Should be applied by the participant under direct supervision of the site staff. Study cream should be applied after PK or translational blood draws on applicable days.
Dispense (D) and return (R) study cream and reminder/diary cards	R/D	R/D	R/D	R/D	R		All tubes of study drug to be weighed before dispensing and when returned. Tubes may not be redispensed.
Collect study cream tubes and collect/review study cream diary cards	X	X	X	X	X		
Assess compliance of study cream	X	X	X	X	X		Compliance is based on the number of applications. Section 6.4
Assess compliance with NB-UVB	X	X	X	X	X		Compliance is based on the number of sessions recorded by the NB-UVB machine. Section 6.4
Safety assessments							
AE assessment*	X	X	X	X	X	X	*If an AE is noted, relevant body systems should be physically examined in a targeted physical exam. Section 8.3.2 Ad hoc photography of skin-related AEs may occur as applicable. Section 8.2.5
Comprehensive physical examination		X			X		Section 8.3.2
Vital signs	X	X	X	X	X	X	Section 8.3.3

Table 4: Schedule of Assessments Week 16 Through End of Study (Continued)

Procedure	Week 16 (± 3 d)	Week 24 (± 7 d)	Week 32 (± 7 d)	Week 40 (± 7 d)	Week 48 (EOT) (± 7 d)	Safety Follow-Up 30 days (EOT*+7 d) (EOS)	Notes *After last application of study cream or last visit.
Efficacy assessments							
F-BSA	X	X	X	X	X	X	Section 8.2.1
T-BSA	X	X	X	X	X	X	Includes facial and nonfacial areas. Section 8.2.1
F-VASI	X	X	X	X	X	X	Section 8.2.2
T-VASI	X	X	X	X	X	X	Includes facial and nonfacial areas. Section 8.2.2
[redacted]							
Photography of face		X		X	X		Section 8.2.5
Photography of nonfacial target area		X		X	X		
[redacted]							
Laboratory assessments							
Hematology and chemistry assessments		X		X	X		Section 8.3.5
Pregnancy testing (serum)						X	Section 8.3.5.1
Pregnancy testing (urine)	X	X	X	X	X		Section 8.3.5.1

Table 4: Schedule of Assessments Week 16 Through End of Study (Continued)

Procedure	Week 16 (± 3 d)	Week 24 (± 7 d)	Week 32 (± 7 d)	Week 40 (± 7 d)	Week 48 (EOT) (± 7 d)	Safety Follow-Up 30 days (EOT*+7 d) (EOS)	Notes *After last application of study cream or last visit.
PK and translational assessments							
PK blood draw	X*						Blood samples must not be drawn from an area that has been treated with study cream. Samples will be drawn at preapplication. Section 8.4 *Only participants starting combination at Week 12.
[redacted]							
Vitamin D assessment		X		X	X	X	
[redacted]							

Note: Unscheduled visits may occur at any time at the investigator's discretion, and appropriate clinical and laboratory tests may be performed, as clinically indicated.

2. INTRODUCTION

2.1. Ruxolitinib Cream

Ruxolitinib cream is in Phase 3 development for the treatment of vitiligo and is a topical formulation of ruxolitinib phosphate, an inhibitor of the JAK family of protein TYKs. Janus kinases are intracellular signaling enzymes that act downstream of key proinflammatory cytokines implicated in vitiligo pathogenesis. Ruxolitinib is a novel, potent, and selective inhibitor of the JAKs, specifically JAK1 and JAK2 with modest to marked selectivity against TYK2 and JAK3. Ruxolitinib potently (IC_{50} < 5 nM) inhibits JAKs, yet it does not significantly inhibit (< 30% inhibition) a broad panel of 26 kinases when tested at 200 nM (approximately 100 times the average IC_{50} value for JAK enzyme inhibition). Ruxolitinib-mediated inhibition of JAK signaling may be an effective strategy for vitiligo treatment.

2.2. Background

Vitiligo is an autoimmune pigmentary disease that is estimated to affect 0.5% to 2% of the population worldwide (Krüger and Schallreuter 2012) and is characterized by depigmented patches of skin with a selective loss of melanocytes. The natural course of the disease is generally unpredictable, but it is often progressive. Some degree of spontaneous repigmentation may occur in 10% to 20% of patients; however, it is typically not cosmetically acceptable (Castanet and Ortonne 1997).

Vitiligo is considered a serious disease owing to its substantial psychological burden on patients and its progressive course if left untreated. Involvement of exposed skin (eg, face and hands) can have a major negative impact on self-esteem and quality of life (Silverberg and Silverberg 2013).

Currently, there is no approved drug treatment for repigmentation in vitiligo. The management of vitiligo is empirical and based on the most recent consensus guidelines (American Academy of Dermatology, Gawkrodger et al 2008, Taieb et al 2013, Vitiligo Research Foundation). In general, first-line treatments consist of topical steroids and calcineurin inhibitors, which may be most useful for treating disease that is localized. However, this use is off-label, there are inconclusive (or insufficient) data supporting their efficacy, many have restrictions on duration of chronic use, and AEs can limit their tolerability. Second-line treatments consist of phototherapy (NB-UVB and PUVA) and systemic steroid treatment. However, phototherapy regimens typically require 2 to 3 treatments per week, and 12 to 24 months of continuous phototherapy may be necessary to acquire maximal repigmentation (Taieb et al 2013); relapses are common. Third-line treatments consist of surgical grafting techniques and depigmenting treatments. Surgery is best indicated for stable and localized forms of vitiligo, and only a small number of patients with vitiligo are considered suitable candidates. All of these treatments can have adverse effects that limit their use.

No available product or therapy is able to modify the course of vitiligo disease and produce a long-lasting effect. Given the lack of approved therapies, safety concerns, and modest effectiveness of current off-label drug treatments, there is a need to identify a safe and effective new treatment for vitiligo.

2.3. Clinical Efficacy and Safety Data With Ruxolitinib Cream

The clinical efficacy and safety of ruxolitinib cream in vitiligo has been evaluated in over 800 participants in 3 randomized, vehicle-controlled studies, 1 Phase 2 (157 participants) and 2 Phase 3 studies (674 participants).

Study INCB 18424-211 evaluated 4 regimens of ruxolitinib cream (1.5% BID, 1.5% QD, 0.5% QD, 0.15% QD) versus vehicle BID for 24 weeks in adults. In INCB 18424-211, all participants initially randomized to vehicle BID and participants initially randomized to 0.15% QD who did not achieve ≥ 25% improvement from baseline in F-VASI25 were rerandomized to 1 of the 3 higher strength groups for an additional 28 weeks. All other participants maintained in the same treatment until Week 52. After Week 52, participants could receive open-label 1.5% BID for an additional 104 weeks. The primary endpoint was the proportion of participants who achieved a ≥ 50% improvement from baseline in F-VASI50 at Week 24.

In Study INCB 18424-211, all ruxolitinib treatment groups demonstrated clinically meaningful efficacy and superiority over vehicle. The proportion of participants who achieved an F-VASI50 at Week 24 was statistically significantly greater for ruxolitinib cream versus vehicle with response rates of 32.3%, 25.8%, 50.0%, and 45.5% for ruxolitinib cream 0.15% QD, 0.5% QD, 1.5% QD, and 1.5% BID, respectively, and 3.1% for vehicle. The proportion of participants who achieved an F-VASI75 at Week 24 was also statistically significantly greater for ruxolitinib cream versus vehicle with response rates of 9.7%, 16.1%, 16.7%, and 30.3% for ruxolitinib cream 0.15% QD, 0.5% QD, 1.5% QD, and 1.5% BID, respectively, and 0% for vehicle.

In Study INCB 18424-211, improvements in T-VASI were observed at both Weeks 24 and 52. The proportion of participants who achieved a T-VASI50 at Week 24 was also statistically significantly greater for ruxolitinib cream 0.15% QD, 0.5% QD, 1.5% QD, and 1.5% BID compared with vehicle with response rates of 16.1%, 6.5%%, 23.3%, and 12.1%, respectively, compared with 0% in vehicle treated participants. Continued improvement in participants treated with 0.5% QD, 1.5% QD, and 1.5% BID through Week 52 was observed with response rates in T-VASI50 of 25.8%, 30.0%, and 36.4%, respectively.

In participants with vitiligo in Study 18424-211, the incidence and severity of TEAEs among participants who applied ruxolitinib cream were generally similar to those in participants who applied vehicle cream during the vehicle-controlled period; 67.2% and 62.5% of participants on active treatment and vehicle, respectively, had at least 1 TEAE; 0.8% and 0% of participants on active treatment and vehicle, respectively, had at least 1 Grade 3 or higher TEAE. The most frequently reported TEAEs in the active treatment groups during the vehicle-controlled period were acne (12.0%), application site pruritus (10.4%), pruritus (8.8%), and viral upper respiratory tract infection (6.4%). The most common events by preferred term occurred at a comparable incidence for participants on vehicle cream with the exception of acne, which was more common in participants on active treatment. With continued exposure for the 3 highest application strength groups, acne (14.9%), pruritus (12.8%), application site pruritus (7.4%), and viral upper respiratory tract infection (10.6%) remained among the most common TEAEs. No serious TEAE had a fatal outcome nor were they considered related to the study cream by the investigator. There were no clinically meaningful changes in chemistry or hematology parameters, and no clinically meaningful changes were noted for vital signs.

In Study INCB 18424-211, after Week 52, a subset of participants were offered optional concomitant NB-UVB phototherapy while continuing open-label treatment with ruxolitinib 1.5% cream BID. Participants could start phototherapy at any time during the open-label period. Nineteen participants received add-on NB-UVB for ≥ 12 weeks (Pandya et al 2021), with 3 times per week being the most common phototherapy regimen. Among these 19 participants, 15 participants (78.9%) had further improvement in F-VASI and 18 participants (94.7%) had further improvement in T-VASI after the addition of NB-UVB to the ruxolitinib cream regimen. Only 4 participants (21%) who received concomitant NB-UVB therapy had AEs, all of which were Grade 1 or 2 in severity and none were related to treatment.

Studies INCB 18424-306 and -307 are identically-designed, randomized, vehicle-controlled, Phase 3 studies in adolescent and adult participants (≥ 12 years old, ~10% of whom were adolescents) with vitiligo. Participants received blinded study treatment for 24 weeks and were then offered the opportunity to receive an additional 28 weeks of treatment with ruxolitinib cream 1.5% BID. NB-UVB therapy was not allowed in the Phase 3 studies.

Both ongoing Phase 3 studies (INCB 18424-306 and -307) studies met the primary endpoint ($p < 0.0001$ for both studies), demonstrating that significantly more participants treated with ruxolitinib cream 1.5% twice daily (BID) achieved a ≥ 75% improvement from baseline in the facial vitiligo area scoring index (F-VASI75) compared to participants treated with a vehicle control at Week 24. Safety and tolerability in the Phase 3 studies were similar to Study INCB 18424-211 in that the rate of Grade 3 TEAEs, SAEs, and TEAEs leading to discontinuation was low. Further, there were no significant TEAEs or application site events and no clinically relevant hematological changes.

2.4. Study Rationale

NB-UVB phototherapy is thought to stimulate the proliferation of melanocytes and melanogenesis, thereby acting in coordination with JAK inhibition, which creates a more favorable immune environment for melanocyte survival by inhibiting the autoimmune response. In Study INCB 18424-211, the addition of phototherapy to ruxolitinib cream in participants with vitiligo was well tolerated; the frequency of adverse events was low, and none were related to treatment (Pandya et al 2021). The addition of NB-UVB phototherapy to ruxolitinib cream resulted in further substantial improvement in repigmentation, including in participants who did not achieve F-VASI50 at Week 24. The current study will investigate these findings in a larger study.

This study is a 2-part, open-label study examining the addition of NB-UVB to ruxolitinib 1.5% cream BID. Approximately 50 participants will receive ruxolitinib 1.5% cream BID for 12 weeks. At Week 12, participants will be assigned to ruxolitinib 1.5% cream alone or in combination with NB-UVB (3 times per week through Week 48) based on the improvement in T-VASI (see Figure 1). Participants who have < T-VASI25 will receive the combination of NB-UVB phototherapy and ruxolitinib 1.5% cream BID (Group A). Participants who have ≥ T-VASI25 at Week 12 will continue on ruxolitinib 1.5% cream BID alone (Group B).

In Study INCB 18424-211, 21.2% of participant who applied ruxolitinib 1.5% cream BID achieved a T-VASI25 at Week 12. T-VASI25 at Week 12 represents a reasonable outcome showing that the participant is having a response to ruxolitinib cream and will potentially benefit from ruxolitinib cream alone. In participants that do not achieve a T-VASI25 at Week 12, NB-UVB will be added to possibly increase the response rate.

NB-UVB phototherapy administered 3 times per week has been chosen as the regimen for this study as this regimen has been shown to induce repigmentation (Mohammad et al 2017). This combination regimen should provide adequate stimulation to the melanocytes to augment the repigmentation provided by ruxolitinib cream alone.

The primary purpose of this study is to evaluate mean percentage change from baseline of T-VASI at Week 48. Additionally, a secondary endpoint is the safety and tolerability of combination therapy (ruxolitinib cream plus NB-UVB) in participants with vitiligo.

2.5. Justification for Strength of Ruxolitinib Cream

Results from Study INCB 18424-211 showed that ruxolitinib 1.5% cream BID had the highest repigmentation rate on both F-VASI and T-VASI, particularly at Week 48. All ruxolitinib treatment strengths were generally safe and well tolerated with no significant TEAEs or application site events and no clinically relevant hematological changes. Also, the available data for phototherapy combination was with ruxolitinib 1.5% cream BID. Further, in the 2 Phase 3 studies, ruxolitinib 1.5% BID showed statistically significant and clinically meaningful improvements for F-VASI and T-VASI compared with vehicle, and the safety profile was similar to that seen in the Phase 2 study.

2.6. Justification for Dose of Narrow-Band Ultraviolet B Phototherapy

NB-UVB phototherapy is an established treatment modality for vitiligo. Recent research suggests that in addition to an immunosuppression effect, NB-UVB stimulates growth and migration of remaining perilesional and follicular melanocytes. A combination of NB-UVB and ruxolitinib cream may lead to an accelerated rate of repigmentation, and potentially a more durable response to treatment.

NB-UVB phototherapy administered 3 times per week (see Table 7) has been chosen as the regimen for this study as this regimen has been shown to induce repigmentation (Mohammad et al 2017); therefore, starting at Week 12 participants who have < T-VASI25 will receive combination therapy of ruxolitinib cream 1.5% BID in combination with NB-UVB phototherapy 3 times per week through Week 48. Participants who have ≥ T-VASI25 at Week 12 will continue to receive ruxolitinib cream monotherapy. This combination regimen should provide adequate stimulation to the melanocytes to augment the repigmentation provided by ruxolitinib cream alone.

2.7. Benefit/Risk Assessment

Results from dermal safety studies to evaluate local tolerability in healthy participants demonstrate that ruxolitinib 1.5% cream did not cause sensitization and was only slightly irritating under exaggerated testing conditions (occlusive application). In addition, ruxolitinib 1.5% cream was not phototoxic and did not induce photosensitization. This was further confirmed by the available safety data in the Phase 2 and Phase 3 studies where ruxolitinib cream was well tolerated at the application sites with infrequently reported application site reactions.

In participants with vitiligo, all ruxolitinib treatment strengths were generally safe and well tolerated with no significant TEAEs or application site events. The TEAE rate overall was low and similar between active treatment and vehicle. Application site acne was noted as an adverse drug reaction in the IB. The rate of TEAEs leading to discontinuation from treatment was low. No serious TEAE had a fatal outcome nor were they considered related to the study cream by the investigator. There were no clinically meaningful changes in chemistry or hematology parameters, and no clinically meaningful changes were noted for vital signs.

A comprehensive analysis of potential safety concerns associated with oral ruxolitinib and other oral JAK inhibitors was performed. As expected given the low bioavailability and the low plasma concentrations of ruxolitinib observed following topical application, ruxolitinib cream was not associated with these safety concerns.

Narrow-band UVB is generally safe and there were no safety issues with the combination in the small subset of participants in Study INCB 18424-211. There are no substantial safety issues expected.

Ruxolitinib cream showed statistically significant and clinically meaningful improvement in participants with vitiligo compared with vehicle. Also, among the 19 participants who received combination therapy with ruxolitinib 1.5% cream and NB-UVB in Study INCB 18424-211, F-VASI and T-VASI improvements after add-on phototherapy increased for all response parameters.

As ruxolitinib 1.5% cream is generally safe and well tolerated and showed clear benefit in the Phase 2 and Phase 3 studies, the benefit risk profile is expected to be positive.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of ruxolitinib cream may be found in the IB.

3. OBJECTIVES AND ENDPOINTS

Table 5 presents the objectives and endpoints.

Table 5: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of ruxolitinib cream in combination with NB-UVB in participants with vitiligo.	• Change from baseline in T-VASI at Week 48.
Secondary	
To evaluate the safety and tolerability of ruxolitinib cream in combination with NB-UVB.	• Occurrence of AEs and evaluation of vital signs and laboratory data.
To further evaluate the efficacy of ruxolitinib cream in combination with NB-UVB in participants with vitiligo.	• Proportion of participants achieving F-VASI50/75/90 at each postbaseline visit. • Proportion of participants achieving T-VASI50/75/90 at each postbaseline visit. • Change and percentage change from baseline in F-VASI/T-VASI at each postbaseline visit. • Change and percentage change from baseline in F-BSA/T-BSA at each postbaseline visit.
To evaluate the ruxolitinib PK in plasma after treatment with ruxolitinib cream in combination with NB-UVB.	• Population-based (trough) plasma concentrations of ruxolitinib at Weeks 4, 12, and 16.

Table 5: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is an open-label study in which participants will apply ruxolitinib 1.5% cream BID to all depigmented areas up to 10% BSA for up to 48 weeks. Participants should continue to treat depigmented areas identified for treatment at baseline regardless of whether the area begins to improve or fully repigment.

On Day 1, all participants will apply ruxolitinib 1.5% cream BID as monotherapy (see Figure 1). At Week 12, participants will apply ruxolitinib 1.5% cream alone or in combination with NB-UVB based on improvement in T-VASI score. Participants who have < T-VASI25 will have NB-UVB phototherapy added to their ruxolitinib 1.5% cream BID regimen (Group A). NB-UVB will be given 3 times per week through Week 48 (36 weeks). Participants who have ≥ T-VASI25 at Week 12 will continue on ruxolitinib 1.5% cream BID alone (Group B). For participants who receive combination therapy, NB-UVB machines will be supplied by the sponsor for at home use during the study.

At any time during the study, if vitiligo areas become significantly more extensive than from the previous visit, the participant should contact the study site to discuss with the investigator whether additional evaluation at the clinic is required. Participants who have expansion of areas of vitiligo identified at baseline or new areas of vitiligo during the course of the treatment period should not treat the additional areas of vitiligo with ruxolitinib cream.

Participants who permanently discontinue NB-UVB will be allowed to remain in the study and continue to apply ruxolitinib 1.5% cream BID alone. Participants who permanently discontinue ruxolitinib 1.5% cream BID will be allowed to remain in the study and continue NB-UVB phototherapy alone.

4.2. Overall Study Duration

The study begins when the first participant signs the study ICF. It is estimated that an individual will participate for approximately 14 months (up to 30 days for screening, up to 48 weeks of treatment, and 30 days for safety follow-up).

A participant is considered to have completed the study if they have completed the 48-week treatment period and the safety-follow-up period. A study is considered completed when the last participant last visit has occurred.

4.3. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The investigator is to notify the IRB/IEC of the study's completion or early termination in writing, send a copy of the notification to the sponsor or sponsor's designee, and retain 1 copy for the site study regulatory file.

The sponsor may terminate the study electively if required by regulatory decision. If the study is terminated prematurely, the sponsor will notify the investigators, the IRBs and IECs, and the regulatory bodies of the decision and reason for termination of the study.

5. STUDY POPULATION

Deviations from eligibility criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or participant safety. Therefore, adherence to the criteria as specified in the Protocol is essential. Prospective approval of Protocol deviations to recruitment and enrollment criteria, also known as Protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Ability to comprehend and willingness to sign a written ICF for the study (or by parent or legally authorized representative).
2. Age ≥ 12 years at the time of signing the ICF.
3. A clinical diagnosis of nonsegmental vitiligo with depigmented area including all of the following:
   a. ≥ 0.5 F-VASI on the face
   b. ≥ 3.0 T-VASI (body areas not including the face)
   c. Total body vitiligo area (facial and nonfacial) not exceeding 10% BSA.
4. Agree to discontinue all agents used to treat vitiligo from screening through the final safety follow-up visit. Over-the-counter preparations deemed acceptable by the investigator and camouflage makeups are permitted.
5. Willingness to take appropriate contraceptive measures to avoid pregnancy or fathering a child for the duration of study participation with the exception of the following:
   a. Female participants of nonchildbearing potential (ie, or surgically sterile with a hysterectomy and/or bilateral oophorectomy OR postmenopausal [≥ 12 months of amenorrhea without an alternative medical cause]).

   Note: Permitted methods in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. No pigmented hair within any of the vitiligo areas on the face.
2. Other forms of vitiligo (eg, segmental) or other differential diagnosis of vitiligo or other skin depigmentation disorders (eg, piebaldism, pityriasis alba, leprosy, postinflammatory hypopigmentation, progressive macule hypomelanosis, nevus anemicus, chemical leukoderma, and tinea versicolor).
3. Used depigmentation treatments (eg, monobenzone) for past treatment of vitiligo or other pigmented areas.

   Note: Prior use of hydroquinone is not prohibited.

4. Previous pruritic, urticarial, morbilliform reaction to NB-UVB phototherapy that caused discontinuation of therapy.
5. Received at least 36 phototherapy sessions for vitiligo within 6 months and shown little or no repigmentation in response to previous phototherapy, including NB-UVB and excimer laser.
6. History of thromboembolic events (eg, deep vein thrombosis, pulmonary embolism, ischemic stroke, myocardial infarction).
7. Concurrent conditions and history of other diseases:
    a. Any other skin disease that, in the opinion of the investigator, would interfere with the study cream application or study assessments.
    b. Active acute bacterial, fungal, or viral skin infection (eg, herpes simplex, herpes zoster, chicken pox) within 1 week before baseline.
    c. Conditions at baseline that would interfere with evaluation of vitiligo.
    d. Any serious illness or medical, physical, or psychiatric condition(s) that, in the investigator's opinion, would interfere with full participation in the study, including application of study cream and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.
    Examples include but are not limited to the following:
        – Clinically significant or uncontrolled cardiac disease, including unstable angina, acute myocardial infarction within 6 months from Day 1 of study cream application, New York Heart Association Class III or IV congestive heart failure, and arrhythmia requiring therapy or uncontrolled hypertension (blood pressure > 150/90 mmHg) unless approved by the medical monitor/sponsor.
        – Concurrent malignant disease or a history of that in the 5 years preceding the baseline visit except for adequately treated nonmetastatic malignancies.
        – Current and/or history of liver disease, including known hepatitis B or C, with hepatic or biliary abnormalities.
        – History of tuberculosis.
        – History of alcohol use disorder or drug addiction within 1 year before screening or current alcohol or drug use that, in the opinion of the investigator, will interfere with the participant's ability to comply with the application schedule and study assessments.
        – Committed to an institution by virtue of an order issued by either the judicial or the administrative authorities.
8. Use of any topical drugs on the vitiligo areas (eg, corticosteroids, calcineurin, and phosphodiesterase type 4 inhibitors or retinoids) within **1 week** before baseline.
9. Use of any of the following treatments within **4 weeks** before baseline:
    a. Melanocyte-stimulating agents (eg, afamelanotide).
    b. Immunomodulating systemic medications (eg, corticosteroids, methotrexate, cyclosporine).

c. Any other systemic therapies that could increase the skin sensitivity to UV/visible light or impact skin pigmentation, for example, tetracyclines, metoxypsoralens.
d. Received live attenuated vaccine.

10. Use of laser or any kind of phototherapy (including tanning bed or intentional UV exposure) within **12 weeks** before baseline.
11. Use of any of the following treatments within **5 half-lives or 12 weeks** (whichever is longer) before baseline:

    a. Biologic agents for the treatment of vitiligo.
    b. Investigational or experimental therapy or procedures for vitiligo.

    Note: Investigational biologics should be discussed with the sponsor to determine whether a longer period of discontinuation is required.

12. Previously received JAK inhibitors, systemic or topical.
13. Any of the following clinical laboratory values at screening:

    a. Hemoglobin (< 10 g/dL).
    b. Liver function tests:

    – AST or ALT ≥ 2 × ULN.

    – Alkaline phosphatase and/or bilirubin > 1.5 × ULN (isolated bilirubin > 1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%).

    c. Severe renal disease (with creatinine clearance < 30 mL/min) or renal disease requiring dialysis.
    d. Clinically significant abnormal TSH or free T4 at screening as determined by the investigator.
    e. Positive serology test results at screening for HIV antibody.

14. Appropriate BMI:

    a. Adults: < 17 or > 40 kg/m^2.
    b. Adolescents (age ≥ 12 to < 18 years): BMI-for-age in the < 5th percentile or ≥ 85th percentile range according to the CDC BMI Percentile Calculator for Child and Teen (CDC).

15. Pregnant or lactating, or those considering pregnancy during the period of their study participation.
16. In the opinion of the investigator are unable or unlikely to comply with the application schedule and study evaluations.
17. Known allergy or reaction to any component of the ruxolitinib formulation.
18. No venous access outside of the areas to be treated.
19. Live with anyone participating in any current Incyte-sponsored ruxolitinib cream study.
20. Employees of the sponsor or investigator or are otherwise dependents of them.

5.3. Lifestyle Considerations

If sunscreen, makeup, or other cosmetics have been applied to the areas to be treated, participants should follow the application guidance (see Section 6.6.1).

Participants should not take baths or showers within 2 hours after study cream application.

It is recommended that swimming should not take place within 2 hours before and after the study cream application.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study.

Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes that the participant would be eligible if retested. Additionally, a participant who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status or any laboratory abnormality is inconsistent with the participant's medical history. Participants who rescreen must reconsent and be assigned a new screening number.

5.5. Replacement of Participants

Participants will not be replaced during the study.

6. STUDY TREATMENT

6.1. Study Treatments Administered

Table 6 and Table 7 present the study treatment information. Participants should apply study cream only to depigmented vitiligo areas identified by the investigator at baseline up to a T-BSA (facial and nonfacial) of ≤ 10% BSA. Participants should continue to treat all depigmented vitiligo areas identified for treatment at baseline regardless of whether the area begins to improve or fully repigment.

On visit days, study cream will be applied in the clinic during the visit. Participants should remove study cream from the tube in fingertip units until all of the areas to be treated are covered by a thin film; the tube will be weighed before and after application to determine the participant's dosage. On the day of a visit, the participant should not apply the study cream at home and will apply study cream from a new kit in the clinic during the visit under direct supervision of the site staff. Participants will be instructed to document the treated areas and be advised to limit use to no more than 1 tube (60 g) per week. Application instructions will be provided by the site study staff, and the participants will record their daily applications via a diary card given to the participants during each study visit. Refer to the Study Pharmacy Manual for participant instructions for handling of study cream.

On days where there are PK or translational assessments, study cream should be applied after these procedures have occurred.

For participants who receive combination therapy, ruxolitinib cream should be applied at least 2 hours before NB-UVB phototherapy.

See Appendix B for application instructions.

At any time, if vitiligo areas become significantly more extensive than from the previous visit, the participant should contact the study site to discuss with the investigator whether additional evaluation at the clinic is required. Participants may not treat the expanded or newly identified areas with study cream. If any other skin products that are permitted under the study Protocol are used, participants should continue these unchanged during the study.

See Appendix C for COVID-19-related guidance.

Table 6: Study Treatment Information (Ruxolitinib Cream)

Study treatment name:	Ruxolitinib
Dosage formulation:	Cream
Mechanism of action:	JAK inhibitor
Unit strength:	1.5%
Route of administration:	Topical
Application instructions:	A thin film is applied BID to depigmented vitiligo areas.
Packaging and labeling:	Ruxolitinib cream will be provided in 60 g tubes. Each tube will be labeled as required per country requirement.
Storage:	Ambient (15°C-30°C/59°F-86°F)
Status of treatment in participating countries:	Investigational

Table 7: Study Treatment Information (NB-UVB)

Study treatment name:	NB-UVB (311-312 nm)
Dosage formulation:	Cleared medical device
Dosage levels:	Starting dose = 200 mJ/cm^2 Increase dose by 10% at each visit until mild erythema lasting < 24 hours as reported by the participant. Hold dose at 1500 mJ/cm^2 – this may vary or be increased over the course of treatment. Dose information will be collected in the database.
Administration instructions:	Three times a week; not on consecutive days.
Status of treatment in participating countries:	Standard of care

6.2. Preparation, Handling, and Accountability

The investigator or designee must confirm and document that appropriate temperature conditions (ruxolitinib cream is to be stored between 15°C and 30°C [59°F-86°F]) have been maintained during transit for all study treatments received and any discrepancies are reported and resolved before use of the study cream.

Only participants enrolled in the study may receive study treatment, and only authorized site staff may supply study cream. Immediately after application of ruxolitinib cream, participants are to wash their hands thoroughly with soap and warm water (unless the area to be treated includes the hands). Refer to the Study Pharmacy Manual for participant instructions for handling of study cream.

All study cream must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. Participants should store study cream at ambient temperature conditions.

The investigator (or designee) is responsible for study cream accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities. The investigator or designee must maintain records that document:

- Delivery of study cream to the study site.
- Inventory of study cream at the site.
- Participant use of the study cream, including tube counts from each supply dispensed.
- Return of study cream to the investigator or designee by participants.

The investigational product must be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that the participants were provided the specified study cream. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study participants.

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study cream until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee shipment of any remaining study cream back to the sponsor or its designee for destruction according to institutional SOPs. If local procedures mandate on-site destruction of investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study cream is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

Further guidance and information for the final disposition of unused study cream are provided in the study materials provided to sites.

6.3. Measures to Minimize Bias: Randomization and Blinding

Not applicable as this is an open-label study.

6.4. Study Treatment Compliance

Compliance with all study-related treatments must be emphasized to the participant by the site personnel, and appropriate steps should be taken to optimize compliance during the study.

Compliance with ruxolitinib cream will be evaluated by participants' adherence to the application regimen and drug accountability documented by the site staff and monitored by the sponsor/designee.

In general, the application compliance will be determined by the number of actual versus anticipated number of applications, which should be within 70% to 130% of the prescribed number of applications. Participants will be instructed to bring all tubes of study cream with them to the study visits in order for site personnel to conduct tube counts to assess study cream accountability. The drug accountability documentation will be used by the sponsor to calculate treatment compliance.

Compliance with NB-UVB will be determined by the number of sessions as recorded by the NB-UVB machine. Participants will be instructed to bring the session recording device with them to the study visits in order for site personnel to conduct the compliance assessment. Site staff must provide source documentation of all treatment dates and details.

6.5. Dose Modifications

6.5.1. Criteria and Procedures for Application Interruptions of Study Cream

Safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue application of study cream.

In some circumstances, it may be necessary to temporarily interrupt application of ruxolitinib cream. Except in cases of emergency, it is recommended that any findings of concern (eg, AE) be confirmed and that the investigator consult with the sponsor medical monitor (or other representative of the sponsor) before interrupting study cream. Additionally, the investigator must obtain approval from the sponsor before restarting study cream. Participants who have a recurrence of the initial AEs upon restarting the study cream and the AE is confirmed related to the study cream may need the study cream to be permanently discontinued.

If a participant has an AE at an application site, application of ruxolitinib cream to that site can be temporarily interrupted without interrupting application of study cream elsewhere.

Instructions for application interruptions for ruxolitinib cream are outlined in Table 8. Individual decisions regarding interruptions should be made using clinical judgment in consultation with the medical monitor (whenever possible), taking into account relatedness of the AE to the study cream and the participant's underlying condition.

If it is unclear whether a skin reaction is related to ruxolitinib cream or the NB-UVB, the investigator should consider interrupting both.

Table 8: Guidelines for Interruption and Restarting of Study Cream

Adverse Event	Action Taken
Chemistry	
ALT (> 3 × ULN) or AST (> 3 × ULN)	• Laboratory abnormalities should be confirmed with repeat testing within 48 hours whenever possible and immediate delivery of the laboratory results requested. • Study cream applications must be interrupted. At the discretion of the investigator, after consultation with the sponsor, study cream application may be restored once these have resolved.
Other laboratory abnormalities	
Any other Grade 3 or higher laboratory abnormality	• Laboratory abnormalities should be confirmed with repeat testing within 48 hours whenever possible and immediate delivery of the laboratory results requested. • Study cream applications must be interrupted. At the discretion of the investigator, after consultation with the sponsor, study cream application may be restored once these have resolved.
Any Grade 4 laboratory abnormality or AST or ALT (> 5 × ULN)	• Laboratory abnormalities should be confirmed with repeat testing within 48 hours whenever possible and immediate delivery of the laboratory results requested. • Discontinue study cream if lab abnormalities are confirmed.

6.5.2. Criteria for Permanent Discontinuation of Study Cream Due to an Adverse Event

The occurrence of unacceptable severity of an AE that is related to study cream application will require that the study cream be permanently discontinued. Unacceptable severity is defined as follows:

- Occurrence of an AE that is related to treatment with the study cream that, in the judgment of the investigator or the sponsor's medical monitor, compromises the participant's ability to continue study-specific procedures or continuing treatment is considered not to be in the participant's best interest.
- Worsening of vitiligo that requires treatment with a prohibited concomitant medication.

See Section 7 for discontinuation procedures.

6.5.3. Dose Modification for NB-UVB

On subsequent treatments, the NB-UVB machine will record participant responses about pinkness/tenderness of the skin during the previous days. Table 9 shows the dose modifications that should occur based on skin reaction. These dose modifications will be programmed into the machine. If there is severe pinkness/redness or there is pain, the participant may need to have an unscheduled visit for the investigator to evaluate the participant. The participant is not to

undergo any further light treatments until it resolves, and treatment can restart at a 15% decreased dose. Once the ordered holding dose is reached, hold at that dose until evaluated by the investigator. The holding dose may be increased at that time.

If it is unclear whether a skin reaction is related to ruxolitinib cream or the NB-UVB, the investigator should consider interrupting both.

If the participant has missed NB-UVB treatments, dose adjustments for missed treatments are listed in Table 10.

Table 9: NB-UVB Dose Adjustments Based on the Skin Assessments

Responses to NB-UVB Machine Question[a]	Skin Assessment	Dose Adjustment
No, or < 24 hours	No erythema reported after last treatment	Increase by 10%
24 – 48 hours	Mild erythema but not painful	Hold dose constant
> 48 hours	Moderate erythema or painful	Decrease by 10%
Still red/pain	Severe, painful erythema	Wait until resolution, decrease dose by 15%

[a] The NB-UVB machine will provide the following question to the participant, "Were you in pain or red after your last treatment?". The participant's response will result in a hold or change to the dose as noted in the dose adjustment column.

Table 10: NB-UVB Dose Adjustments for Missed Treatments

Length of Time Since Previous Dose	Dose Adjustment
Up to 1 week	Maintain dose
1-2 weeks	Decrease by 25% to a minimum of 200 mJ/cm^2
2-3 weeks	Decrease by 50% to a minimum of 200 mJ/cm^2
3-4 weeks	Decrease by 75% to a minimum of 200 mJ/cm^2
> 4 weeks	Restart at 200 mJ/cm^2

6.6. Concomitant Medications and Procedures

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines, and/or herbal supplements) must be recorded in the eCRF. Any medication or procedure received up to 12 weeks before baseline through 30 days after the last application of study cream will be recorded in the eCRF. Any addition, deletion, or change in the dose of these medications will also be recorded.

Other relevant medications or procedures received more than 12 weeks before the first application of study cream may be recorded in the eCRF at the discretion of the investigator or at the request of the sponsor based on emerging events during the study.

If a participant has an SAE, concomitant medications administered more than 30 days after the last application of study cream for treatment of the SAE should be reported until the SAE is no longer being followed (see Section 9.3).

6.6.1. Permitted Medications and Procedures

The following are permitted during the study with application guidance. Investigators and site staff are expected to use their best clinical judgment with these recommendations and adhere to the guidelines as closely as possible. Please consult the sponsor if there are specific questions.

- Participants may use bland emollients or camouflage makeups.

  Note: Emollients or camouflage makeups should not be used within 2 hours after study cream application. The study cream should be applied before sunscreens and camouflage makeup. It is also recommended these be removed from the skin before application of the study cream. Any makeup remover must then be washed off and the skin dried before application of the study cream.

- If sunscreen is needed, a mineral-based sunscreen (such as zinc oxide– or titanium oxide–based) with SPF of at least 30 is recommended 2 hours after study cream application and/or NB-UVB phototherapy.

  Note: Sunscreen must be removed from the skin before study cream application if it has been applied to the areas to be treated.

- Participants who receive combination therapy should apply ruxolitinib cream at least 2 hours before NB-UVB phototherapy.

- Concomitant oral vitamins and other skin products should be approved by the investigator and ideally should remain stable during the study.

6.6.2. Restricted Medications and Measures

The following are restricted during the study under specified conditions:

- Use of any over-the-counter, nonprescription preparations (including vitamins, minerals, and phytotherapeutic, herbal, or plant-derived preparations) within 7 days before the baseline visit through the safety follow-up visit, unless deemed acceptable by the investigator.

- Use of any prescription medication (including immunizations, phytotherapeutic, herbal, or plant-derived preparations) within 7 days before the baseline visit through the safety follow-up visit, unless deemed acceptable by the investigator.

- Baths or showers within 2 hours after study cream application.

- Treatment for dermatologic disease besides vitiligo (eg, AD or psoriasis) is allowed for areas not being treated for vitiligo, if:

  – It involves < 10% of the BSA outside of the areas treated for vitiligo.

  – Topical tacrolimus, pimecrolimus, or corticosteroids Class 6 or 7 (or low potency per WHO classification; see Appendix C) are at a stable dose.

  – Topical corticosteroids Class 1 through 5 (see Appendix C) are used for no longer than 7 sequential days and no more than 14 days in total.

- Use of oral corticosteroids for no longer than 7 days if deemed acceptable by the investigator and the sponsor for nondermatologic conditions (eg, asthma exacerbation, bronchitis).

6.7. Prohibited Medications and Procedures

Participants should not use any other treatments for vitiligo at any time during the study. The following medications are not permitted during the study:

- Any investigational medication other than the study cream
- Treatment known to affect the course of vitiligo, such as skin bleaching treatments (eg, hydroquinone) or depigmenting agents (eg, monobenzone)

  Note: Skin bleaching (eg, hydroquinone) use is prohibited during the study but is allowed as prior therapy.
- Other topical agents (except those in Section 6.6.1) or treatments for vitiligo (including corticosteroids [topical, systemic, or oral], vitamin D derivatives, calcineurin inhibitors, laser or surgical treatments, phototherapy, or other procedures).
- Biological therapies or other immunosuppressant agents
- Any phototherapy other than that prescribed as part of the study
- Use of a tanning bed
- Receipt of a live vaccine during the course of the study and within 4 weeks after the EOT visit

6.8. Treatment After the End of the Study

Upon completion of the 48 weeks of treatment, participants will not be provided additional treatment within this study.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

Participants **must** be discontinued from study treatment for the following reasons:

- The participant becomes pregnant.
- Consent is withdrawn.
  Note: Consent withdrawn means that the participant has explicitly indicated that they do not want to be followed any longer; in this case, no further data (except data in public domain) may be solicited from or collected regarding the participant. Participants may choose to discontinue application of study cream and remain in the study to be followed for safety.

- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- Any AE of unacceptable severity as noted in Section 6.5.2.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

A participant **may** be discontinued from study treatment as follows:

- A participant is found not to have met eligibility criteria (any exclusion criterion or any inclusion criteria related to participant safety) or if legal requirements have been violated.
- If, at 2 consecutive study visits, a participant's study cream usage exceeds 1 tube (60 g) per week.
- If a participant is noncompliant with study procedures or study cream application in the investigator's opinion, the medical monitor should be consulted for instruction on handling the participant.

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the application of study cream, an EOT visit should be conducted. Reasonable efforts should be made to have the participant return for a safety follow-up visit. The last date of the last application of study cream and the reason for discontinuation of study cream will be recorded in the eCRF.

If a participant is discontinued from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal must be documented in the participant's medical record and the primary reason for withdrawal must be included in the eCRF.
- The EOT visit should be performed.
- The date of the EOT visit should be recorded in the eCRF.
- Participants must be followed for safety until the time of the safety follow-up visit or until study cream/treatment–related AEs resolve, return to baseline, or are deemed irreversible, whichever is longest.

If the participant discontinues application of study cream and actively withdraws consent for collection of follow-up data (safety follow-up or disease assessment), then no additional data collection should occur; however, participants will have the option of withdrawing consent for study treatment but continuing in the safety follow-up period.

7.2. Participant Withdrawal From the Study

A participant may withdraw from the study at any time at their own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, they may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

See Table 3 and Table 4 for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. The participant will be counseled regarding the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

See Appendix C for COVID-19-related guidance.

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

- The investigator or their representative will explain the nature of the study to the participant or their legally authorized representative and answer all questions regarding the study.
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.

    Note: Adolescent participants who become legal adults during the study will be asked for their signed consent to continue the study, and in the event of lack thereof, will be discontinued from further participation.
  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the participant. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to participant records.
  - The ICF must contain all required elements and describe the nature, scope, and possible consequences of the study in a form understandable to the study participant.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the countries in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must provide consent to the most current version of the ICF during their participation in the study.

- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

8.1.2. Screening Procedures

Screening is the interval between signing the ICF and the day that the participant is assigned to the study cream (Day 1). Screening assessments for determination of eligibility may be performed over a period lasting up to 30 days.

Procedures conducted as part of the participant's routine clinical management (eg, clinical laboratory tests) and collected before informed consent is obtained may be used for screening or baseline purposes, provided the procedure meets the Protocol-defined criteria and has been performed within 30 days before Day 1. All information associated with eligibility requirements, including demography and medical history, must be entered into the appropriate eCRF pages.

Results from the screening assessments will be reviewed by the investigators to confirm eligibility before Day 1 and application of study cream. Tests results that fail eligibility requirements may be repeated once during screening if the investigator believes that the participant would be eligible if retested. For screening assessments that are repeated, the most recent available result before application of study cream will be used to determine eligibility.

See Sections 5.4 and 5.5 for information regarding screen failures and replacement of participants, respectively.

8.1.3. Interactive Response Technology Procedure

Each participant will be identified in the study by a participant ID number, which is a combination of the 2-letter alpha ISO country code, 3-digit site ID, and 3-digit participant number. Site personnel should contact the IRT system to obtain the participant ID number during screening. Upon determining that the participant is eligible for study entry, the IRT system will be contacted to obtain the study treatment kit assignment. Additionally, the IRT system will be contacted at each regular study visit to update the study cream supply. Additional details are provided in the IRT Manual.

8.1.4. Distribution of Study Reminder Cards and Diaries

Starting at the Day 1 visit and each visit thereafter, a study cream–specific diary will be given to each participant in order to record use of the study cream. The completed diary will be collected during each of the participant's visits.

Qualified clinical site staff will review the participants' entries for compliance. Participants who are noncompliant with their study cream schedule (defined as < 70% or > 130% of the expected number of applications between study visits) will have their application instructions reinforced by the investigator or a qualified designee. Participants will be considered compliant with the treatment regimen if they apply at least 70% but no more than 130% of the expected applications during participation in the treatment period of the study.

Participants will be provided with a reminder card starting on Day 1 and at all visits (through Week 48). The reminder card will indicate the date/time of the next visit and will also remind the participant that they should have their application at the clinic during the visit under site supervision after their blood draws for PK and safety evaluations have been completed.

8.1.5. Demography and Medical History

8.1.5.1. Demographics and General Medical History

Demographic data and general medical history will be collected at screening by the investigator or qualified designee and will include year of birth/age, race, ethnicity, medical and surgical history, and current illnesses. Medical history will include relevant medical or surgical treatment within the last 2 years that are considered to be clinically significant by the investigator.

8.1.5.2. Disease Characteristics and Treatment History

Vitiligo medical and treatment history, including date of diagnosis, relevant disease characteristics, and prior treatments, including systemic treatments, phototherapy, and surgical procedures, will be recorded. Medical history of other conditions related to vitiligo will also be collected at screening.

8.2. Efficacy Assessments

8.2.1. Body Surface Area

Total BSA (includes facial and nonfacial areas) depigmented by vitiligo will be estimated at each visit. Body surface area assessment will be performed by the Palmar Method. The BSA should be estimated to the nearest 0.1%. The approximate size of the participant's entire palmar surface (ie, the palm plus 5 digits) should be considered as 1% BSA, and the approximate size of the participant's thumb should be considered as 0.1% BSA.

Facial BSA (F-BSA) takes into account the facial depigmented areas as a percentage of the total body area.

Total BSA (T-BSA) takes into account the depigmented areas for each of the following body regions: head/neck (including scalp), upper extremities (including axillae), hands, trunk (including genitalia), lower extremities (including buttocks), and feet.

F-BSA and T-BSA will be assessed at visits listed in Table 3 and Table 4.

8.2.2. Vitiligo Area Scoring Index

Areas affected by depigmentation due to vitiligo will be assessed using the VASI (Hamzavi et al 2004). It is based on a composite estimate of the overall area of vitiligo patches at baseline and the degree of macular repigmentation within these patches over time. Facial VASI is measured by percentage of vitiligo involvement (%BSA) and the degree of depigmentation. The %BSA (hand unit) vitiligo involvement is estimated by the investigator using the Palmar Method (see Section 8.2.1). Hand unit is based on participant's hand size. The investigator uses their hand to mimic the participant's hand size to evaluate %BSA vitiligo involvement. 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. 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).

The area "face" is defined as including the area on the forehead to the original hairline, on the cheek to the jawline vertically, 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.

Total body VASI is calculated using a formula that includes contributions from all body regions (possible range, 0-100) as follows:

$$\text{VASI} = \sum_{\text{all body sites}} [\text{hand units}] \times [\text{residual depigmentation}]$$

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 percentage of vitiligo involvement is estimated in hand units (%BSA) by the same investigator during the entire course of the study. Hand unit is based on participant's hand size. The investigator uses their hand to mimic the participant's hand size to evaluate %BSA vitiligo involvement. The degree of depigmentation for each body site is determined and estimated to the nearest of the following percentages: 0, 10%, 25%, 50%, 75%, 90%, or 100%. The T-VASI is then derived by multiplying the values assessed for the vitiligo involvement by the percentage of affected skin for each body site and summing the values of all body sites together.

F-VASI and T-VASI will be assessed at visits listed in Table 3 and Table 4. Full details on the conduct of these assessments will be provided in the Study Manual.

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[redacted]

[redacted]

[redacted]

[redacted]

8.2.5. Photography

Photography of the face and/or body areas affected with vitiligo will be obtained at visits listed in Table 3 and Table 4.

All sites will use 2-dimensional photography to photograph areas of the participant's face affected with vitiligo and 2 target nonfacial depigmented areas.

Target nonfacial vitiligo depigmented area definition: At the screening visit, depigmented nonfacial areas that are representative of the participant's overall disease will be selected as targeted nonfacial vitiligo depigmented areas. These areas will be assessed, measured, and documented in the participant's medical record at each subsequent visit during the study (see Table 3 and Table 4). A note should be made in their medical record, and the baseline photographs can be marked with the location of the target-depigmented area. The genitalia area should not be photographed.

If photo quality at screening is not adequate, the photography may be repeated on Day 1. The baseline photos are defined as the adequate ones either taken at screening or Day 1.

Ad hoc photography of skin-related AEs is recommended.

Photographic procedures will be standardized, and a full description of the methodology will be provided in a photography manual to be provided to the sites.

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8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in Table 3 and Table 4.

See Section 6.5 for guidelines regarding the management of relevant laboratory or other safety assessment abnormalities.

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 30 days after the last application of study cream. Adverse events for enrolled participants that begin or worsen after informed consent should be recorded on the Adverse Event Form in the eCRF regardless of the assumption of a causal relationship with the study cream. Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study cream/procedures, or that caused the participant to discontinue the study cream or NB-UVB. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open ended and nonleading verbal questioning of the participant, such as "How are you feeling?", is the preferred method to inquire about AE occurrences. Adverse events may also be detected when they are volunteered by the participant during the screening process or between visits or through physical examinations, laboratory tests, or other assessments. The definition, reporting, and recording requirements for AEs are described in Section 9.

All SAEs will be reported to the sponsor or designee within 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

8.3.2. Physical Examinations

Physical examinations will be conducted at the timepoints listed in Table 3 and Table 4.

A comprehensive physical examination will include height and body weight and assessment of the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes. A brief neurologic examination will also be performed.

A targeted physical examination should only be conducted as indicated by symptoms reported by the participant, AEs, or other findings. Abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

Physical examinations must be performed by a medically qualified individual such as a licensed physician, a physician's assistant, or an advanced registered nurse practitioner, as local law permits.

8.3.3. Vital Signs

Vital sign measurements will be conducted at the timepoints listed in Table 3 and Table 4.

Vital sign measurements include blood pressure, pulse, respiratory rate, and body temperature. Blood pressure and pulse will be taken with the participant in the recumbent, semirecumbent, or sitting position after 5 minutes of rest. Any abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

8.3.4. Electrocardiograms

Electrocardiograms will be performed at screening or if deemed clinically necessary.

A single 12-lead ECG will be obtained at screening (12-lead ECG performed within 2 months before baseline is acceptable) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. All 12-lead ECGs will be performed with the participant in a recumbent or semirecumbent position after 5 minutes of rest.

The decision to include or exclude a participant or withdraw a participant from the study treatment based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

8.3.5. Laboratory Assessments

Required laboratory tests are listed in Table 13. See Table 3 and Table 4 for timing of assessments. Clinical laboratory tests will be performed at a central laboratory (refer to the Laboratory Manual for sample handling and shipping instructions).

Clinically significant abnormal laboratory findings are those that induce clinical signs or symptoms, require concomitant therapy, or require changes in study cream or NB-UVB. All laboratory tests with values considered clinically significantly abnormal during participation in the study, or within 30 days after the last application of study cream, should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

See Section 9.1 for information regarding laboratory abnormalities that should be recorded as an AE in the eCRF.

Table 13: Required Laboratory Analytes

<table>
<tr><th>Serum Chemistries[a]</th><th>Hematology</th><th>Urinalysis</th><th>Serology</th><th>Other</th></tr>
<tr><td rowspan="3">Albumin
Alkaline phosphatase
ALT
AST
Bicarbonate
Blood urea nitrogen
Calcium
Chloride
Creatine kinase
Creatinine
Glucose
Lactate dehydrogenase
Phosphate
Potassium
Sodium
Total bilirubin
Direct bilirubin (if total bilirubin is elevated above ULN)
Total protein</td><td rowspan="3">Complete blood count, including:
• Hemoglobin
• Hematocrit
• Mean corpuscular volume (MCV)
• Platelet count
• Mean platelet volume
• Red blood cell count
• Reticulocyte count
• White blood cell count

Differential count, including:
• Basophils
• Eosinophils
• Lymphocytes
• Monocytes
• Neutrophils</td><td>Color and appearance
pH and specific gravity
Bilirubin
Glucose
Ketones
Leukocytes
Nitrite
Occult blood
Protein
Note: Abnormal results should be microscopically examined.</td><td>HIV antibody</td><td>FSH[b]
Free T4
TSH
Vitamin D2 and D3</td></tr>
<tr><td colspan="2">Pregnancy Testing</td></tr>
<tr><td colspan="2">Female participants of childbearing potential will undergo a serum test at the screening and safety follow-up visits. A urine test will be conducted at all other visits. A positive urine test will be confirmed by a serum test.</td></tr>
</table>

Note: Additional tests may be required, as agreed by investigator and sponsor, based on emerging safety data or to rule out a diagnosis.

[a] All serum chemistries will be performed on samples collected without respect to food intake (ie, nonfasting).

[b] FSH is only measured for postmenopausal women (defined by amenorrhea for ≥ 12 months without an alternative medical cause before screening); FSH should be in the postmenopausal range to consider the participant of nonchildbearing potential.

8.3.5.1. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential during screening and at the safety follow-up visit (30 [+ 7] days after EOT). Urine pregnancy tests will be conducted as outlined in Table 3 and Table 4, as medically indicated, or per country-specific requirement. Urine pregnancy tests will be performed locally. If a urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test, which may be performed locally.

If the serum pregnancy test is negative after a urine test was positive, the investigator will assess the potential benefit/risk to the participant and determine whether it is in the participant's best interest to resume study cream and continue participation in the study.

If a pregnancy is confirmed by a serum pregnancy test, see Section 9.7 for reporting requirements.

8.3.5.2. Serology

An HIV antibody assessment will be performed at the screening visit to rule out infection (see Table 3). Serology tests should be performed early in the screening process due to the length of time needed to obtain the results. Additional tests may be performed if clinically indicated.

8.4. Pharmacokinetic Assessments

Venous blood samples will be collected as indicated in Table 3 and Table 4 to assess the PK of ruxolitinib cream in this study population.

The exact date and time of the PK blood draws and the date and time of the last application of study cream before the blood draw (if applicable) will be recorded in the eCRF.

Instructions for sample preparation and shipping will be provided in the Laboratory Manual. Participants will receive reminder cards in advance of the study visit providing instruction to hold the application of study cream on the day of the visit and a place to record the time of the prior application of study cream.

Pharmacokinetic blood samples can be collected before application of study cream during study visits noted in the Table 3 and Table 4. Blood samples must not be drawn from the area that has been treated with study cream. If it is not possible to access an area that is not treated with study cream, the site must adequately document this in the eCRF and not take the PK blood sample for that visit. After the PK sample is drawn, participants will apply ruxolitinib cream 1.5% at the site.

All analyses will be conducted by Incyte Corporation (Wilmington, DE) or Incyte's designee.

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8.6. Unscheduled Visits

Unscheduled visits may occur at any time at the investigator's discretion, and appropriate clinical and laboratory tests may be performed, as clinically indicated.

8.7. End of Treatment and/or Early Termination

If a decision is made that the participant will permanently discontinue application of study cream, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, then the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT page in the eCRF. If this decision does not coincide with a regular visit, reasonable efforts should be made to have the participant return to the site to have the EOT procedures completed.

8.8. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled safety follow-up visit, which should occur 30 (+ 7) days after the EOT visit (or after the last application of study cream if an EOT visit was not performed).

Adverse events and SAEs must be reported up until at least 30 days after the last application of study cream/treatment. Adverse events and SAEs must be followed until toxicities resolve, return to baseline, or are deemed irreversible. Reasonable efforts should be made to have the participant return for the safety follow-up visit and report any AEs that may occur during this period.

9. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

9.1. Definition of Adverse Event

Adverse Event Definition
• An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered drug-related. • An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study cream.
Additional Guidance for Events Meeting the Adverse Event Definition
• Any safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease) are to be reported as an AE. • Abnormal laboratory test results are to be reported as an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study cream. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal laboratory test result (eg, low hemoglobin, platelet count decreased). • Exacerbation of a chronic or intermittent pre-existing condition/disease, including either an increase in the frequency and/or intensity of the condition, is to be reported as an AE. • New conditions detected or diagnosed after the start of study cream application are to be reported as an AE. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction are to be reported as an AE. • Signs and/or symptoms from application errors of a study cream (eg, overdose) or a concomitant medication are to be reported as an AE. • "Lack of efficacy," "disease progression," or "failure of expected pharmacological action" will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. • A condition that leads to a medical or surgical procedure (eg, endoscopy, appendectomy) will be reported as an AE if it occurs after obtaining informed consent. The procedure should also be reported in the eCRF. If the condition was present before entering the study, then it should be captured as medical history. • Pre-existing diseases or conditions with expected fluctuations in signs or symptoms should be reported as an AE only if the investigator judges the fluctuation to have worsened more than expected during study participation.

9.2. Definition of Serious Adverse Event

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an adverse drug experience that places the participant, in the opinion of the initial reporter, at immediate risk of death from the adverse experience as it occurs. This does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment or planned surgery (eg, stent replacement, hip surgery) is not considered an SAE.

Hospitalization for medical interventions in which no unfavorable medical occurrence occurred (ie, elective procedures or routine medical visits) are not considered SAEs.

d. Results in persistent or significant disability/incapacity

- The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is an important medical event

An important medical event is an event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such events include new invasive or malignant cancers, intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. Secondary malignancies should always be considered SAEs.

9.3. Recording and Follow-Up of Adverse Events and/or Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- An AE/SAE that begins or worsens after informed consent is signed should be recorded on the Adverse Event Form in the eCRF. AEs/SAEs should be reported for enrolled participants, but only SAEs need to be reported for screen failure participants. For enrolled participants, conditions that were present at the time informed consent was given should be recorded on the Medical History Form in the eCRF. For detailed information, refer to the eCRF guidelines.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator (or delegate) will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completing the Adverse Event Form in the eCRF.
- There may be rare instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted by the site staff on the copies of the medical records before submission. These records can be submitted to Incyte Pharmacovigilance by email/fax per the contact information listed in the Study Reference Manual or as per SAE completing guidelines.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE/SAE.

To the extent possible, each AE/SAE should be evaluated to determine the following:

- The severity grade (CTCAE v5.0 Grade 1 to 5). See below for further instructions on the assessment of intensity.
- Whether there is at least a reasonable possibility that the AE is related to the study cream: suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at the final safety follow-up visit.
- The action taken with regard to study cream as a result of the AE/SAE(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on the Adverse Event Form, and the treatment should be specified on the appropriate eCRF (eg, Prior/Concomitant Medications, Procedures and Non-Drug Therapy).

Assessment of Intensity

The severity of AEs will be assessed using CTCAE v5.0 Grades 1 through 5. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity.

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study cream and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are medical facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the possibility of a relationship.
- The investigator will also consult the RSI in the IB or Product Information for ruxolitinib cream, or marketed products, respectively, in making their assessment.
- Alternative causes, such as underlying or concurrent disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study cream application, will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that they has reviewed the AE/SAE and has provided an assessment of causality.
- With regard to assessing causality of SAEs:
  - There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, the causality assessment is one of the criteria used when determining regulatory reporting requirements. **Therefore, it is very important that the investigator always make an assessment of causality based on the available information for every event before the initial transmission of the SAE.**
  - The investigator may change their opinion of causality in light of follow-up information and submit the updated causality assessment.

Follow-Up of Adverse Events and Serious Adverse Events
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • Once an AE is detected, it should be followed in the AE eCRFs until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study cream, the interventions required to treat the event, and the outcome. • When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings, including histopathology. • Updated SAE information will be recorded in the originally completed eCRF and reported to Incyte Pharmacovigilance (via the AE and SAE eCRFs in the EDC) until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. • Any updated SAE data (including SAEs being downgraded to nonserious) will be submitted to the sponsor (or designee) within 24 hours of receipt of the information.

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study cream, study procedures), all SAEs occurring after the participant has signed the ICF through the last safety visit or at least 30 days after the last application of study cream must be reported to the sponsor (or designee) immediately, without undue delay, but not later than within **24 hours** of obtaining knowledge of its occurrence unless otherwise specified by the Protocol. The investigator will submit any updated SAE data to the sponsor (or designee) immediately, without undue delay, but not later than within 24 hours of it being available.

Investigators are not obligated to actively seek SAE information after the safety follow-up visit or 30 days after the last application of study cream. If the investigator learns of any SAE, including death, at any time during this period, and the event is considered to be reasonably related to the study cream or study participation, the investigator must notify the sponsor (or designee) within 24 hours of becoming aware of the event.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

Prompt notification by the investigator to the sponsor regarding an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study cream under clinical investigation are met.

If the SAE is not documented in the RSI of the IB for the study cream (new occurrence) and is thought to be related to the study cream, the sponsor or its designee may urgently require further information from the investigator for expedited reporting to health authorities. The sponsor or its

designee may need to issue an Investigator Notification to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected unexpected serious adverse reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study cream under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Serious Adverse Event Reporting
• Information about all SAEs is collected and recorded on the Adverse Event Form in the eCRF. • The investigator must report within 24 hours of learning of its occurrence any SAE via the EDC system (primary method) or by completing the Serious Adverse Event Report Form in English (only if the EDC system is not available). The contact information for Incyte Pharmacovigilance by email/fax is listed in the Study Reference Manual or as per the Incyte Reference Guide for Completing the Serious Adverse Event Report Form. • In circumstances where the EDC system is not accessible for reporting SAE information (initial and/or follow-up SAE information) to the sponsor within 24 hours, refer to the Incyte Reference Guide for Completing the Serious Adverse Report Form. Once the EDC system is functional, the SAE report should be retrospectively added to the EDC system and follow-up should be completed through the EDC. The original copy of the Serious Adverse Event Report Form and the email or facsimile confirmation sheet must be kept at the study site (refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form or Study Reference Manual for details and for the email address or fax number). • Follow-up information is also recorded in the eCRF and transmitted to Incyte Pharmacovigilance via the EDC system. The follow-up report should include information that was not provided previously, such as the outcome of the event, treatment provided, action taken with study cream because of the SAE (eg, application amount reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.

9.5. Events of Clinical Interest

Not applicable.

9.6. Emergency Unblinding of Treatment Assignment

Not applicable.

9.7. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that the study cream may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed in a participant during maternal or paternal exposure to study cream, the following procedures should be followed in order to ensure safety:

- The study cream must be discontinued immediately (female participants only).
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy Form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

Data on fetal outcome are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study cream to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form or Study Reference Manual.

Any SAE occurring during pregnancy of a study participant must be recorded on the Serious Adverse Event Report Form and submitted to the sponsor or its designee.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, or ectopic pregnancy) are considered SAEs (if occurring in the study participant) and must be reported as described in Section 9.4 . If an abnormal pregnancy outcome is reported in a study participant's partner, the event should be reported to the sponsor on the Clinical Trial Pregnancy Form.

9.8. Warnings and Precautions

Special warnings or precautions for the study cream, derived from safety information collected by the sponsor or its designee, are presented in the IB. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. Any important new safety information should be discussed with the participant during the study as necessary. If new significant risks are identified, they will be added to the ICF.

9.9. Product Complaints

The sponsor collects product complaints on study cream and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

All product complaints associated with material packaged, labeled, and released by the sponsor or its designee will be reported to the sponsor. All product complaints associated with other study material will be reported directly to the respective manufacturer.

The investigator or their designee is responsible for reporting a complete description of the product complaint via email or other written communication to the sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be recorded as described in Section 9.3.

If the investigator is asked to return the product for investigation, they will return a copy of the product complaint communication with the product.

9.10. Treatment of Overdose

There has been no clinical experience with overdose of ruxolitinib cream. Treatment of overdose should consist of general supportive measures.

NB-UVB can result in skin burning similar to sunlight. If the participant experiences skin burning from the NB-UVB device, they should apply emollients and contact the study site for instructions on how to treat the skin reaction.

10. STATISTICS

10.1. Sample Size Determination

Due to the exploratory nature of the study, there will be no statistical hypothesis test between the 2 treatment groups, and the sample size is not based on statistical power calculations. The sample size is considered to be sufficient to obtain adequate efficacy, safety, tolerability, and PK data to achieve the objectives of the study.

10.2. Populations for Analysis

Table 14 presents the populations for analysis.

Table 14: Populations for Analysis

Population	Description
FAS	The FAS includes all participants enrolled in the study who applied study cream at least once. The FAS will be used for the summary of demographics, baseline characteristics, participant disposition, and analyses of all efficacy and safety data.
PK evaluable	The PK evaluable population includes participants who applied study cream at least once and provided at least 1 postapplication blood sample for PK. The study pharmacokineticist will review data listings of participant application and sample records to identify participants to be excluded from the analysis.
Pharmacodynamic evaluable	The pharmacodynamic evaluable population includes participants who applied study cream at least once and provided at least 1 postapplication blood sample for translational assessment. The study translational scientist will review data listings of participant application and sample records to identify participants to be excluded from the analysis.

10.3. Level of Significance

This is an exploratory study, and no formal statistical tests will be performed. All confidence intervals will be 95%.

10.4. Statistical Analyses

The Statistical Analysis Plan will be developed and finalized before database lock and will describe the details of the statistical analyses and procedures for accounting for missing data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

10.4.1. Efficacy Analysis

All efficacy assessments will be summarized using descriptive statistics at each visit for FAS.

10.4.1.1. Analysis of Primary Efficacy Analysis

The primary efficacy endpoint is the change from baseline in T-VASI at Week 48. For the primary endpoint, summary statistics will include sample size, mean, median, standard deviation, minimum, maximum, and the 95% confidence interval.

10.4.1.2. Analysis of Secondary Efficacy Endpoints

10.4.1.2.1. Continuous Efficacy Endpoints

By-visit summary statistics for the following continuous measurements, including actual measurement, change from baseline, and percentage change from baseline, will be presented:

- F-VASI/T-VASI
- F-BSA/T-BSA

Summary statistics, including sample size, mean, median, standard deviation, minimum, maximum, first quartile, third quartile, and 95% CI, will be presented by visits.

10.4.1.2.2. Categorical Efficacy Endpoints

For the following categorical parameters, summary statistics will include sample size, frequency, percentages and standard error of percentage, and the 95% confidence interval at each visit.

- Proportion of participants achieving F-VASI50/75/90
- Proportion of participants achieving T-VASI50/75/90

10.4.2. Safety Analysis

Safety is being evaluated as a secondary objective in this study. Safety analyses will be conducted using the safety population and are summarized in Table 15.

Table 15: Safety Analyses

Endpoint	Statistical Analysis Methods
Secondary	**Adverse Events** A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first application of study cream. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study cream application. Adverse events will be coded using MedDRA and tabulated by preferred term and system organ class. Severity of AEs will be based on the CTCAE v5.0 using Grades 1 through 5. The subset of AEs considered by the investigator to have a relationship to study cream will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study cream, then the AE will be considered treatment-related. The incidence of AEs and treatment-related AEs will be tabulated. **Clinical Laboratory Tests** Actual values and changes from baseline in clinical laboratory test results will be summarized using descriptive statistics. Laboratory test values outside the normal range will be assessed for severity based on the normal ranges for the clinical reference laboratory. The incidence of abnormal laboratory values will be tabulated. Laboratory data will be classified into Grades 1 through 5 using CTCAE v5.0. Shift tables from baseline to the worst postbaseline value using CTCAE grade will be tabulated. **Vital Signs** Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, pulse, respiratory rate, and body temperature) at each assessment time.

10.4.3. Other Analyses

Pharmacokinetic endpoints are listed in Section 8.4. Pharmacokinetic analyses will be performed using the PK evaluable population. The INCB018424 plasma concentration data will be analyzed by descriptive summary analysis.

Translational endpoints are listed in Section 8.5. Details of translational analyses will be provided in the Statistical Analysis Plan.

10.5. Interim Analysis

No formal interim analysis is planned in this study.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

- The Protocol, Protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC and Health Authorities, before the study is initiated.
- The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements, the policies and procedures established by the IRB/IEC, and institutional requirements.
- Any amendments to the Protocol will require approval from both Health Authorities and IRB/IEC before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to GCP, IRB/IEC requirements, institutional requirements, and applicable laws and country-specific regulations.
- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling participants who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.

- All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

11.1.1. Identification of the Coordinating Principal Investigator

A coordinating principal investigator will be appointed by the sponsor before the end of the study. As part of his or her responsibilities, the coordinating principal investigator will review the final CSR. Agreement with the final CSR will be documented by the dated signature of the coordinating principal investigator.

11.2. Data Management

Data management will be performed in a validated EDC system. The investigator will be provided with access to an EDC system so that an eCRF can be completed for each participant.

The site will be provided with eCRF completion guidelines for instructions on data entry in the eCRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue identified is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements. Other data outside the EDC system required in the study conduct of the Protocol such as documents or results transmitted to the sponsor via a central laboratory or specialized technical vendors and, as designated by the sponsor, will have their own data flow management plans, study charters, or [redacted], as applicable.

The sponsor (or designee) will be responsible for:

- Managing the integrity of the data and the quality of the conduct of the study, such as ensuring that study monitors perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved Protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Managing and reconciling the data generated, and/or collected including documents and results such as laboratory or imaging data analyzed centrally by a designated vendor of the sponsor.

The investigator will be responsible for:

- Recording, or ensuring the recording of, all relevant data relating to the study in the eCRF.
- Delivering, or ensuring the delivery of, all other results, documents, data, know-how, or formulas relating to the study to the sponsor or designee electronically and/or centrally (eg, laboratory data, imaging data, [redacted], photographs, diary data), or as otherwise specified in the Protocol.
- Maintaining adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants. Source data should be

attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source data are in general all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

- Verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Maintaining accurate documentation (source data) that supports the information entered in the eCRF, or sent to a central vendor designated by the sponsor, or as described in other study and data flow manuals.
  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed and available at the investigator's site. Examples of source documents are original documents, data, and records (eg, hospital records, electronic hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participants' files, and e-records/records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).
  - Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current applicable medical records must be available.
- Sending participants' data, either as unique samples, or copies, or photographs, to be evaluated centrally or analyzed centrally, or both, by a qualified vendor designated by the sponsor.
- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and participant records at each monitoring visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all participants.

- Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.

11.3. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data protection laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that sensitive personal information is handled in accordance with local data protection laws (including but not limited to HIPAA and GDPR) as applicable. Appropriate consent for collection, use and disclosure and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws.

Participant names will not be supplied to the sponsor or its designee. Only the participant number will be recorded in the eCRF; if the participant's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with appropriate technical and organizational measures as required by local data protection laws.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 10 years after study completion unless local regulations require otherwise. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

11.4. Financial Disclosure

Before study initiation, all clinical investigators participating in clinical studies subject to FDA Regulation Title 21 CFR Part 54 – Financial Disclosure by Clinical Investigators (ie, "covered studies") are required to submit a completed Clinical Investigator Financial Disclosure form that sufficiently details any financial interests and arrangements that apply. For the purpose of this regulation, "clinical investigator" is defined as any investigator or subinvestigator who is directly involved in the treatment or evaluation of research participants, including the spouse and each dependent child of the clinical investigator or subinvestigator. These requirements apply to both US and foreign clinical investigators conducting covered clinical studies.

Any new clinical investigators added to the covered clinical study during its conduct must also submit a completed Investigator Financial Disclosure Form. During a covered clinical study, any changes to the financial information previously reported by a clinical investigator must be reported to the sponsor or its designee. At the conclusion of the covered clinical study, the clinical investigators will be reminded of their obligations. In the event that the clinical investigator is not reminded, they nevertheless will remain obligated to report to the sponsor or its designee any changes to the financial information previously reported, as well as any changes in their financial information for a period of 1 year after completion of the covered clinical study.

11.5. Publication Policy

By signing the study Protocol, the investigator and their institution agree that the results of the study may be used by the sponsor, Incyte Corporation (Incyte), for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. Study results will be published in accordance with applicable local and national regulations. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. The terms regarding the publication of study results are contained in the agreement signed with the sponsor or its designee. A signed agreement will be retained by the sponsor or its designee.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined in line with International Committee of Medical Journal Editors authorship requirements.

11.6. Study and Site Closure

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the Protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study treatment development.

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS AND DEFINITIONS

Definitions

WOCBP: A woman who is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal with 1 of the following:[a]
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal, highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

For male participants of reproductive potential[b]

The following methods during the Protocol-defined timeframe in Section 5.1 are highly effective:

- Use of a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
- Vasectomy with medical assessment of the surgical success (verified by site personnel's review of the participant's medical records)
- Sexual abstinence[c]
  - Abstinence from penile-vaginal intercourse

The following are **not** acceptable methods of contraception:

- Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method.
- Male condom with cap, diaphragm, or sponge with spermicide.
- Male and female condom used together.

Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

For female participants who are WOCBP

The following methods during the Protocol-defined timeframe in Section 5.1 that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation.[d]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[d]
  - oral
  - injectable
  - implantable[e]
- Intrauterine device[e]
- Intrauterine hormone-releasing system[e]
- Bilateral tubal occlusion[e]
- Vasectomized partner[e,f]
- Sexual abstinence[c]

[a] Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
[b] If the male participant has a partner with childbearing potential the partner should also use contraceptives.
[c] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.
[d] Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.
[e] Contraception methods that in the context of this guidance are considered to have low user dependency.
[f] Vasectomized partner is a highly effective method of avoiding pregnancy provided that partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has received medical assessment of the surgical success.
Source: Clinical Trials Facilitation and Coordination Group (2020).

APPENDIX B. INSTRUCTION TO PARTICIPANTS FOR HANDLING RUXOLITINIB CREAM

The participant must be instructed in the handling of study cream as follows:

- Store study cream at room temperature.
- Make every effort to apply study cream on schedule.
- Report any missed applications.
- Keep study cream in a safe place and out of reach of children.
- Bring all used and unused study cream tubes to the site at each visit.
- Remove study cream from the tube in fingertip units until all of the areas to be treated are covered by a thin film.
- Do not apply study cream on visit days as it will be applied at the site under supervision of the site staff.
- Do not use more than 1 tube (60 g) per week.
- Emollients, sunscreen, or camouflage makeups should not be used within 2 hours after study cream application.
- Do not apply study cream over sunscreen or camouflage makeup. These must be removed from the skin before application of the study cream. Any makeup remover must then be washed off and the skin dried before application of the study cream.
- Participants should not take baths or showers within 2 hours after study cream application.

APPENDIX C. COVID-19 PANDEMIC MITIGATION STRATEGIES AND INSTRUCTIONS

The COVID-19 global pandemic presents numerous challenges to the ongoing conduct of clinical trials. In line with the European Medicines Agency Guidelines on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic (2020), the sponsor has issued the following Protocol considerations to ensure participant safety is maintained and adequate benefit/risk analyses are applied relative to the completion of study procedures and maintaining the investigational product supply chain.

Recognizing the flexibility required to manage the impact of the pandemic on this clinical trial, additional details will be added to respective study manuals and project plan documents and communicated to the investigative sites as needed.

Study Site Visits

If local travel restrictions, isolation requirements, or the investigator's benefit/risk assessment determines it to be unsafe for participants to attend study visits at the investigational site, the site staff may elect to pursue the following:

- In order to minimize participant risk, study visits (except Day 1, Week 4, Week 12, and Week 16 visits) may be conducted via telemedicine modalities (phone or video). At a minimum, a review of AEs, concomitant medications, and study drug compliance must be completed. Periodic on-site visits should be conducted whenever feasible. The physician efficacy assessments must not be conducted by phone or video.
- Day 1, Week 4, and Week 16 visits must be conducted in person in their entirety because translational samples and physician efficacy assessments must be conducted in person. Also, the Week 12 visit must be conducted in person, as this is the assessment for possible addition of NB-UVB phototherapy. These visits cannot be missed or conducted remotely. The investigator should document visit-window deviations in the eCRF if necessary. If an out-of-window deviation is significant (ie, > 4 weeks out-of-window), the investigator should contact the sponsor for discussion and further instructions.

Investigational Medicinal Product Dispensing and Distribution

In order to ensure the continuity of providing their participants' clinical supplies within the constraints imparted by the pandemic, the site staff can decide to supply study drug to participants. Adequate supplies of study drug as determined by the investigator can be shipped to the participants by the investigator or appropriately delegated staff (eg, the study pharmacy staff) using a third-party service if duly authorized by the participant. The study site may use their own preferred courier, provided the courier adheres to certain standards (eg, use of personal protection equipment, maintenance of temperature-controlled transit environment), or one centrally contracted by the sponsor.

Clinical Trial Monitoring

Study monitoring visits may be postponed; however, the site monitor will continue to employ off-site monitoring practices such as routine communication methods (eg, phone calls, emails,

video visits) with the sites to get information on trial progress, participant status, and information on issue resolution. The study monitor may remotely review data entered into the EDC for accuracy and completeness. Remote source data verification may be implemented with agreement of the principal investigator and institution, as applicable.

If the study-site monitor cannot be on-site to perform the final drug accountability for reconciliation purposes, and the operation cannot be postponed, it may be performed by a pharmacist from the hospital pharmacy or by the study coordinator/data manager with suitable training. The study drug can be returned to the sponsor by the hospital pharmacy directly, or it can be destroyed in accordance with local practices, if applicable, and with sponsor approval.

APPENDIX D. WHO CLASSIFICATION OF TOPICAL CORTICOSTEROIDS

Hydrocortisone and betamethasone are examples of low- and high-potency topical corticosteroids. Topical corticosteroids have been ranked in terms of potency into 4 groups consisting of 7 classes. Class I topical corticosteroids are the most potent, and Class VII are the least potent. Efficacy and side effects are greatest with the Class I ultra-high–potency preparations, which should only be used for limited time periods (2-3 weeks). Representative preparations by group are listed in the table below. These groups may vary depending on the formulation and concentration and should be considered approximate. In general, ointments are more potent than creams or lotions. Potency is also increased when topical corticosteroids are used under occlusive dressings or in intertriginous areas.

Potency	Class	Topical Corticosteroid	Formulation
Ultra high	I	Clobetasol propionate	Cream, 0.05%
		Diflorasone diacetate	Ointment, 0.05%
High	II	Amcinonide	Ointment, 0.1%
		Betamethasone dipropionate	Ointment, 0.05%
		Desoximetasone	Cream or ointment, 0.025%
		Fluocinonide	Cream, ointment or gel, 0.05%
		Halcinonide	Cream, 0.1%
	III	Betamethasone dipropionate	Cream, 0.05%
		Betamethasone valerate	Ointment, 0.1%
		Diflorasone diacetate	Cream, 0.05%
		Triamcinolone acetonide	Ointment, 0.1%
Moderate	IV	Desoximetasone	Cream, 0.05%
		Fluocinolone acetonide	Ointment, 0.025%
		Fludroxycortide	Ointment, 0.05%
		Hydrocortisone valerate	Ointment, 0.2%
		Triamcinolone acetonide	Cream, 0.1%
	V	Betamethasone dipropionate	Lotion, 0.02%
		Betamethasone valerate	Cream, 0.1%
		Fluocinolone acetonide	Cream, 0.025%
		Fludroxycortide	Cream, 0.05%
		Hydrocortisone butyrate	Cream, 0.1%
		Hydrocortisone valerate	Cream, 0.2%
		Triamcinolone acetonide	Lotion, 0.1%
Low	VI	Betamethasone valerate	Lotion, 0.05%
		Desonide	Cream, 0.05%
		Fluocinolone acetonide	Solution, 0.01%
	VII	Dexamethasone sodium phosphate	Cream, 0.1%
		Hydrocortisone acetate	Cream, 1%
		Methylprednisolone acetate	Cream, 0.25%

Source: WHO 1997.

APPENDIX E. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Not applicable.

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Approval	[redacted] Approver [redacted]
Approval	[redacted] Approver [redacted]
Approval	[redacted] Approver [redacted]
Approval	[redacted] Approver [redacted]
Approval	[redacted] Approver [redacted]

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