Official Title: A Randomized, Double-Blind, Vehicle-Controlled Study to Evaluate the Mechanism of Action of Ruxolitinib Cream for Vitiligo (TRuE-V MOA)

NCT Number: NCT04896385

Document Date: Original Protocol: 03-March-2021

Clinical Study Protocol

INCB 18424-214

A Randomized, Double-Blind, Vehicle-Controlled Study to Evaluate the Mechanism of Action of Ruxolitinib Cream for Vitiligo (TRuE-V MOA)

Product:	**Ruxolitinib Cream**
IND Number:	[redacted]
EudraCT Number:	**2021-000361-32**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, Delaware, USA 19803**
Original Protocol:	**03 MAR 2021**

INVESTIGATOR'S AGREEMENT

I have read the INCB 18424-214 Protocol (dated 03 MAR 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)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice daily
BSA	body surface area
CFR	Code of Federal Regulations
COVID-19	coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
CXCL	C-X-C motif chemokine ligand
DNA	deoxyribonucleic acid
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
F-VASI	facial Vitiligo Area Scoring Index
F-VASI50/75	50%/75% improvement in facial Vitiligo Area Scoring Index
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IEC	independent ethics committee

Abbreviations and Special Terms	Definition
IFN-γ	interferon gamma
IRB	institutional review board
IRT	interactive response technology
ITT	intent to treat
JAK	Janus kinase
MedDRA	Medical Dictionary for Regulatory Activities
MOA	mechanism of action
PBMC	peripheral blood mononuclear cell
[redacted]	[redacted]
QD	once daily
RNA	ribonucleic acid
RNAseq	ribonucleic acid sequencing
RSI	reference safety information
SAE	serious adverse event
SoA	schedule of activities
SOP	standard operating procedure
SPF	sun protection factor
T4	thyroxine
T-BSA	total body surface area
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
T-VASI	total body Vitiligo Area Scoring Index
T-VASI50/75	50%/75% improvement in total body Vitiligo Area Scoring Index
ULN	upper limit of normal
UV	ultraviolet
VASI	Vitiligo Area Scoring Index
WHO	World Health Organization

1. PROTOCOL SUMMARY

Protocol Title: A Randomized, Double-Blind, Vehicle-Controlled Study to Evaluate the Mechanism of Action of Ruxolitinib Cream for Vitiligo (TRuE-V MOA)

Protocol Number: INCB 18424-214

Objectives and Endpoints:

Table 1 presents the primary and secondary objectives and endpoints.

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the change in immune biomarkers in participants with vitiligo.	• Percentage change from baseline in immune biomarkers, including CXCL10, at Week 4, Week 12, and Week 24.
Secondary	
• To correlate the change in key serum and skin biomarkers of vitiligo to efficacy.	• Correlation of key skin inflammatory biomarkers of vitiligo in target lesions to efficacy readouts at Week 12 and Week 24.
• To assess the safety and local tolerability of ruxolitinib cream.	• The frequency and severity of AEs.

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	Treatment of patients with vitiligo
Population	Male and female participants aged ≥ 18 years of age who have nonsegmental vitiligo with depigmented areas including ≥ 0.5% BSA on the face, ≥ 0.5 F-VASI, ≥ 3% BSA on nonfacial areas, and ≥ 3 T-VASI. Total body vitiligo area (facial and nonfacial) should not exceed 50% BSA.
Number of Participants	Approximately 60 participants will be randomized 2:1 (ruxolitinib cream 1.5% BID:vehicle BID).
Study Design	Randomized, double-blind, vehicle-controlled, with an open-label treatment extension.
Estimated Duration of Study Participation	Screening: Up to 42 days. Double-blind period: 24 weeks. Open-label period: 28 weeks. Safety follow-up: 30 days after last application of study drug or last study visit. Total: Up to approximately 63 weeks.
DSMB	No
Coordinating Principal Investigator	To be determined

Treatment Groups and Duration:

This is a randomized, double-blind, vehicle-controlled study with an open-label treatment extension period in adult participants (age ≥ 18 years) with nonsegmental vitiligo who have depigmented areas including ≥ 0.5% BSA on the face, ≥ 0.5 F-VASI, ≥ 3% BSA on nonfacial areas, and ≥ 3 T-VASI. Total body involved vitiligo area (facial and nonfacial) should not exceed 50% BSA. Approximately 60 participants will be randomized 2:1 to receive initial double-blind study treatment (ruxolitinib cream 1.5%:vehicle) administered BID for 24 weeks (see Figure 1). Participants will be stratified by age (≤ 40 years old and > 40 years old). During the double-blind treatment period, the participant's randomized treatment will be applied to depigmented areas on the face and body up to 20% T-BSA (facial and nonfacial).

After completion of the Week 24 assessments from the double-blind treatment period, eligible participants will be offered the opportunity to continue the study in the 28-week open-label treatment extension period in which all participants will receive open-label ruxolitinib cream 1.5%, administered BID. To be eligible for the open-label treatment extension period, participants must have completed the baseline and Week 24 visit assessments, be compliant with study procedures, and not have any safety issues. The total treated area in the open-label treatment extension period should not exceed 20% BSA (facial and nonfacial).

Figure 1 presents the study design schema. The SoA is detailed in Table 3 (for the double-blind treatment period) and Table 4 (for the open-label treatment extension period). Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Figure 1: Study Design Schema

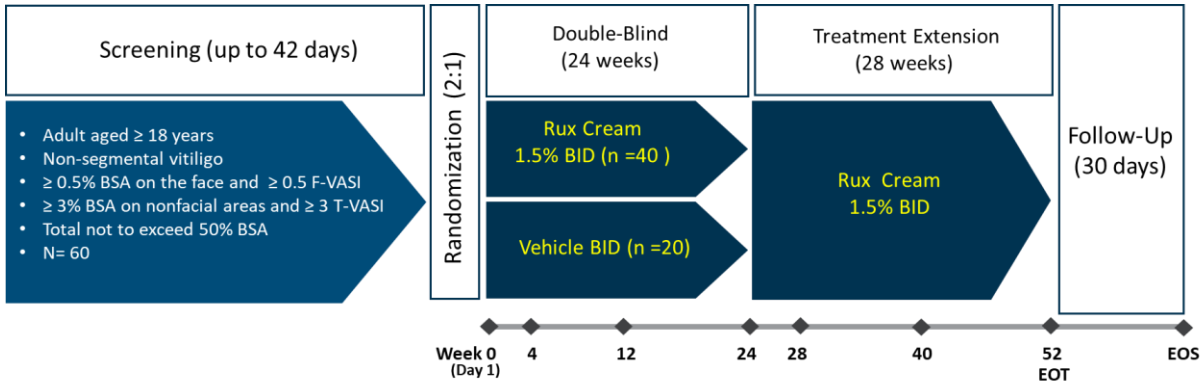

Table 3: Schedule of Activities: Double-Blind, Vehicle-Controlled Treatment Period (Day 1 to Week 24)

Procedure	Screening	Double-Blind, Vehicle-Controlled Treatment						Notes
	Days −42 to −1	Day 1 (Baseline)	Wk 4 (± 3 d)	Wk 8 (± 3 d)	Wk 12 (± 3 d)	Wk 18 (± 7 d)	Wk 24[a] (EOT1) (± 7 d)	
Administrative procedures								
Informed consent	X							
Contact IRT	X*	X	X	X	X	X	X	*Entry of age into the IRT will be required at screening.
Inclusion and exclusion criteria	X	X						
Demography	X							
General and disease medical history	X							
Prior/concomitant medications	X	X	X	X	X	X	X	
Application of study drug at site		X	X	X	X	X	X*	At each study visit, starting at Day 1, the participant should apply the study drug under direct supervision of the site staff. *At the Week 24 visit, study drug is only applied by participants continuing in the open-label treatment extension period.
Dispense (D) and return (R) study drug and reminder/diary cards		D	R/D	R/D	R/D	R/D	R/D*	All tubes of study drug will be weighed before being dispensed. All returned tubes of study drug will be weighed. *At the Week 24 visit, study drug and diary cards are only dispensed to participants continuing in the open-label treatment extension period.
Collect study drug and collect/review study drug diary cards			X	X	X	X	X	
Assess compliance			X	X	X	X	X	

Table 3: Schedule of Activities: Double-Blind, Vehicle-Controlled Treatment Period (Day 1 to Week 24) (Continued)

Procedure	Screening	Double-Blind, Vehicle-Controlled Treatment						Notes
	Days −42 to −1	Day 1 (Baseline)	Wk 4 (± 3 d)	Wk 8 (± 3 d)	Wk 12 (± 3 d)	Wk 18 (± 7 d)	Wk 24[a] (EOT1) (± 7 d)	
Safety assessments								
AE assessment	X	X	X	X	X	X	X	
Comprehensive physical examination	X						X	
Targeted physical examination		X	X	X	X	X		See Section 8.3.2.
Vital signs	X	X	X	X	X	X	X	
12-Lead ECG	X							12-Lead ECG performed within 2 months before baseline is acceptable.
[redacted]								
Laboratory assessments								
Hematology and chemistry assessments	X	X	X	X	X	X	X	
Serology	X							Serology includes hepatitis and HIV assessments.
Thyroid testing	X							
Urinalysis	X							
FSH	X*							*FSH is only measured for confirmation of nonchildbearing status of women who are postmenopausal, defined as having amenorrhea for at least 12 months without an alternative medical cause before screening.
Pregnancy testing	X*	X	X	X	X	X	X	*Female participants of childbearing potential will have 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 must be confirmed by a serum test.

Table 3: Schedule of Activities: Double-Blind, Vehicle-Controlled Treatment Period (Day 1 to Week 24) (Continued)

Procedure	Screening	Double-Blind, Vehicle-Controlled Treatment						Notes
	Days −42 to −1	Day 1 (Baseline)	Wk 4 (± 3 d)	Wk 8 (± 3 d)	Wk 12 (± 3 d)	Wk 18 (± 7 d)	Wk 24[a] (EOT1) (± 7 d)	
[redacted] **translational assessments**								
[redacted]								
Serum biomarker sampling		X	X		X		X	
[redacted]								
Skin biopsy: lesional vitiligo skin (identified at baseline [Day 1])		X			X		X	For lesional skin, [redacted] per timepoint will be taken from the inside edge of an active vitiligo lesion, and the sampling area should be entirely contained within lesional skin. See Section 8.5.1.
Skin biopsy: nonlesional		X						For nonlesional skin, [redacted] will be taken at baseline (Day 1) from uninvolved skin adjacent to the lesional area selected for biopsy.

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.
[a] Week 24 is considered the first visit of the open-label period.

Table 4: Schedule of Activities: Open-Label Treatment Extension (Week 28 to Week 52)

Procedure	Open-Label Treatment Extension			Safety Follow-Up	Notes
	Wk 28 (± 7 d)	Wk 40 (± 7 d)	Wk 52 (EOT2[a]) (± 7 d)	30 Days After EOT1/EOT2[b] (EOS) (+ 7 d)	
Administrative procedures					
Contact IRT	X	X	X	X	
Prior/concomitant medications	X	X	X	X	
Application of study drug at site	X	X			At each study visit, the participant should apply the study drug under direct supervision of the site staff.
Dispense (D) and return (R) study drug and reminder/diary cards	R/D	R/D	R		All tubes of study drug will be weighed before being dispensed. All returned tubes of study drug will be weighed.
Collect study drug and collect/ review study drug diary cards	X	X	X		
Assess compliance	X	X	X		
Safety assessments					
AE assessment	X	X	X	X	
Comprehensive physical examination			X		
Targeted physical examination	X	X		X	See Section 8.3.2.
Vital signs	X	X	X	X	
[redacted]					
Laboratory assessments					
Hematology and chemistry assessments	X	X	X	X	
Pregnancy testing	X	X	X	X*	*Female participants of childbearing potential will have 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 must be confirmed by a serum test.
[redacted] **translational assessments**					
[redacted]					

Table 4: Schedule of Activities: Open-Label Treatment Extension (Week 28 to Week 52) (Continued)

Procedure	Open-Label Treatment Extension			Safety Follow-Up	Notes
	Wk 28 (± 7 d)	Wk 40 (± 7 d)	Wk 52 (EOT2[a]) (± 7 d)	30 Days After EOT1/EOT2[b] (EOS) (+ 7 d)	
[redacted] translational assessments (continued)					
Serum biomarker sampling		X	X*		*Only for participants who stop treatment before Week 52 and do not complete the Week 40 visit.
[redacted]					
Skin biopsy: lesional vitiligo skin (identified at baseline [Day 1])		X	X*		For lesional skin, [redacted] per timepoint will be taken from the inside edge of an active vitiligo lesion, and the sampling area should be entirely contained within lesional skin. See Section 8.5.1. *Only for participants who stop treatment before Week 52 and do not complete the Week 40 visit.

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.

[a] EOT2 assessments should be performed in the event a participant's treatment is stopped before Week 52 at any relevant study visit before that time.

[b] After last application of study drug or last visit.

2. INTRODUCTION

2.1. Background

Ruxolitinib cream is a topical formulation of ruxolitinib phosphate under development for the treatment of patients with atopic dermatitis, alopecia areata, plaque psoriasis, and vitiligo. Ruxolitinib phosphate is an inhibitor of the JAK family of protein tyrosine kinases. Inflammatory cytokines are strongly implicated in the pathogenesis of several dermatologic diseases. Because JAKs serve to translate extracellular signals from a number of relevant cytokines and growth factors upregulated in inflammatory diseases such as atopic dermatitis, alopecia areata, plaque psoriasis, and vitiligo, JAK inhibitors represent potential therapeutic agents for these disease states (Howell et al 2019).

Nonclinical pharmacology, PK, pharmacodynamic, and toxicology data for ruxolitinib cream from in vitro and in vivo model systems support the use of topically applied ruxolitinib cream in the treatment of patients with atopic dermatitis, psoriasis, vitiligo, and other inflammatory diseases of the skin. Refer to the ruxolitinib cream IB for a summary of findings from the nonclinical studies.

Vitiligo is an autoimmune disease that is characterized by areas of depigmented skin; it affects up to 2% of the global population and is associated with a significantly reduced quality of life (Krüger and Schallreuter 2012). Currently, there are no US FDA-approved treatments for vitiligo, and most treatment paradigms rely on the use of corticosteroids, narrowband UV light, off-label treatments, or combination therapy; these treatments produce unpredictable and inconsistent results and are frequently cosmetically unacceptable to the patient. A treatment that produces predictable results and that can be applied by the patient is an area of high unmet need for patients with vitiligo.

The skin of patients with vitiligo is characterized by depigmented patches that result from the infiltration of affected areas with activated antigen-specific CD8+ T cells that drive melanocyte death and disease pathogenesis (Taïeb and Picardo 2009, van den Boorn et al 2009). Recruitment of autoreactive $CD8^+$ T cells to melanocytes is mediated by IFN-γ through the IFN-γ–induced chemokines CXCL9 and CXCL10, a signaling pathway regulated by JAK1 and JAK2 (Harris et al 2012, Rashighi et al 2014, Rashighi and Harris 2015). The interruption of IFN-γ signaling via the JAK pathway represents an important therapeutic strategy to evaluate in the treatment of vitiligo (Dina et al 2019). In a recent randomized, double-blind, placebo-controlled Phase 2 study (INCB 18424-211; NCT03099304), ruxolitinib cream, a topical JAK1/2 inhibitor, demonstrated efficacy in patients with vitiligo (Rosmarin et al 2020; see also Section 2.2.2 for a brief summary of findings from this study). The specific impacts of ruxolitinib cream on the biology of melanocytes were not evaluated in this study, but the findings warrant an evaluation of the effects of ruxolitinib cream on melanocytes and support continued clinical development of ruxolitinib cream for the treatment of patients with vitiligo.

Safety findings from this Phase 2 study and 2 ongoing Phase 3 studies (INCB 18424-306 and INCB 18424-307) in participants with vitiligo also support continued development of ruxolitinib cream for the treatment of patients with this condition. As of the cutoff date for the ruxolitinib cream IB (Edition 9), a total of 203 participants with vitiligo have received ruxolitinib cream.

Safety findings across the 3 vitiligo studies showed that the majority of participants had good local tolerability with use of ruxolitinib cream, there were few application site reactions (all Grade 1 or 2), and all SAEs were reported in 1 participant each (ie, there were no patterns of SAEs).

Refer to the ruxolitinib cream IB for a summary of available clinical efficacy and safety data from the vitiligo studies as well as safety data from ruxolitinib cream clinical studies conducted in other disease states.

2.2. Study Rationale

Three studies have been previously initiated to evaluate the safety and efficacy of ruxolitinib cream in patients with vitiligo: Phase 2 study INCB 18424-211, ongoing Phase 3 study INCB 18424-306 (TRuE-V1), and ongoing Phase 3 study INCB 18424-307 (TRuE-V2); [redacted]. The purpose of the present study is to provide a more comprehensive evaluation than has been undertaken in the previously initiated studies of the MOA of ruxolitinib cream in vitiligo.

2.2.1. Scientific Rationale for Study Design

Janus kinases are intracellular signaling enzymes that act downstream of key proinflammatory cytokines implicated in the pathogenesis of vitiligo. The safety and efficacy of topical cream containing ruxolitinib, a JAK inhibitor, was evaluated in a randomized, double-blind, vehicle-controlled Phase 2 study conducted in adults with vitiligo; the study has completed. Findings from the Phase 2 study demonstrated that treatment with ruxolitinib cream was associated with substantial repigmentation of vitiligo lesions up to 52 weeks of treatment, and all doses were well-tolerated (Rosmarin et al 2020). The Phase 2 data suggest that JAK inhibition is an effective therapeutic strategy to treat patients with vitiligo. Two identical Phase 3 studies were initiated to confirm the Phase 2 findings in a larger patient population and are ongoing.

The objectives of the current Phase 2 MOA study are to collect data that will contribute to the understanding of immune biomarkers of vitiligo and to further confirm the safety and efficacy of ruxolitinib cream in patients with vitiligo. Skin biopsies, serum, and PBMCs will be collected over time to further understand the effect of ruxolitinib cream [redacted] and to assess various biomarkers of inflammation.

The population to be studied comprises adults (≥ 18 years of age) with nonsegmental vitiligo who have depigmented areas including ≥ 0.5% BSA on the face, ≥ 0.5 F-VASI, ≥ 3% BSA on nonfacial areas, and ≥ 3 T-VASI. Total body involved vitiligo area (facial and nonfacial) should not exceed 50% BSA.

Participants enrolled in this study will be randomized 2:1 to receive ruxolitinib cream 1.5% BID or vehicle BID and treated for 24 weeks in a double-blinded fashion. After 24 weeks, participants originally randomized to vehicle will switch to active treatment with ruxolitinib cream. [redacted] Additionally, it is deemed unethical and impractical to deprive patients of

effective management of their skin disease for periods extending beyond a maximum of 6 months. In the Phase 2 study, up to 56.7% of the population was classified as having progressive disease, and long vehicle-controlled periods may have resulted in extension of their disease. The vast majority of clinical studies in chronic nonfatal skin diseases do not use a placebo/vehicle arm for longer than 16 weeks. The proposed 24 weeks is thus a compromise between the longest acceptable duration of no active treatment (vehicle) and the minimum time required to observe a meaningful clinical response to treatment (repigmentation). Additionally, the 2:1 (versus a 1:1) randomization allows more of the study population to receive active treatment for the full duration of the study.

The 28-week open-label period is designed to allow participants initially randomized to vehicle treatment to receive active drug and to further evaluate the [redacted] safety of ruxolitinib cream 1.5% BID treatment.

[redacted]

2.2.2. Justification for Dose

The dose that will be investigated in the current study is ruxolitinib cream 1.5% BID. This is the dose that was selected for evaluation in the Phase 3 vitiligo studies based on findings from the completed Phase 2 study (INCB 18424-211) conducted in adults with vitiligo, which evaluated 4 dose strengths of ruxolitinib cream (1.5% BID, 1.5% QD, 0.5% QD, and 0.15% QD). The safety and efficacy outcomes from the Phase 2 study can be summarized as follows:

- All ruxolitinib cream treatment arms (1.5% BID, 1.5% QD, 0.5% QD, and 0.15% QD) demonstrated efficacy and superiority over vehicle in F-VASI50 and F-VASI75 at Week 24, with a clear separation from vehicle emerging by Week 12.
- At Week 24, 1.5% QD and BID treatment regimens further separated from the 0.15% and 0.5% treatment regimens, with the highest response at Week 24 in F-VASI50 (50.0%) in the 1.5% QD regimen.

- The 1.5% BID treatment regimen demonstrated the highest response for F-VASI75 at both Week 24 (30.3%) and Week 52 (51.5%). The T-VASI50 response in the 1.5% BID regimen was modest at Week 24 (12.1%); however, this regimen also demonstrated the highest response for T-VASI50 (36.4%) at Week 52, and it is recognized that repigmentation on nonfacial areas proceeds slower than on facial areas.
- All ruxolitinib treatment arms were generally safe and well-tolerated with no significant TEAEs or application site events and no clinically relevant hematologic changes through Week 52.

Based on the above data, the treatment regimen of ruxolitinib cream 1.5% BID was chosen for the current Phase 2 MOA study.

2.3. Benefit/Risk Assessment

In nonclinical studies, ruxolitinib cream did not act as a contact sensitizer and did not produce significant dermal irritation or demonstrate phototoxicity or photoallergic potential. The lack of adverse cutaneous effects has been supported by clinical studies to date, where cutaneous AEs have been infrequent and of similar frequency and severity as with vehicle control treatment. Long-term immune suppression may occur with JAK inhibition, which could potentially increase the risk of cutaneous viral skin infections and nonmelanoma skin cancers. Participants should be monitored accordingly.

The primary clinical risks noted with orally administered ruxolitinib for the treatment of polycythemia vera or myelofibrosis are the potential sequelae of decreased hematopoietic proliferation secondary to the inhibition of growth factor pathways by JAK2 antagonism. Dose-dependent, reversible thrombocytopenia has been observed in participants with myelofibrosis, as well as anemia and less frequently neutropenia. An increased rate of infection is an additional potential risk of immunomodulation. In healthy participants and participants with rheumatoid arthritis with greater bone marrow reserve, the effects on hematopoietic proliferation appear to be less pronounced. Owing to its low systemic bioavailability, topical ruxolitinib cream is not expected to bring about clinically significant changes in hematology laboratory investigations.

Results from the Phase 2 study (INCB 18424-211) conducted in adults with vitiligo have been reported (Rosmarin et al 2020), and key findings from this study are summarized in Section 2.2.1. Based on the Week 24 and Week 52 results, all active treatment groups were found to have no clinically relevant AEs related to the treatment regimens and were well-tolerated on application sites. Safety findings from this study were also unremarkable for laboratory values, vital signs, or physical examinations. While minor changes in select hematology parameters (red blood cells and platelet counts) were noted in the laboratory assessments, they were mostly within the limits of the normal range of values, transient, asymptomatic, and clinically insignificant and did not necessitate any remedial action.

Currently, there are no approved therapies for vitiligo, and treatments are empirical and directed by the available clinical guidelines. Current therapies often do not lead to satisfactory response, and there are limitations and safety concerns with long-term use of some therapies, including

topical or oral corticosteroids and calcineurin inhibitors. Given the psychosocial burden and stigma that has been reported in this disease, patients with vitiligo warrant access to new studies.

In summary, ruxolitinib cream 1.5% BID can be safely used as a topical medication for vitiligo and represents the treatment regimen with the best benefit-to-risk ratio from among those investigated.

More detailed information about the known and expected benefits and risks and reasonably expected AEs 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 change in immune biomarkers in participants with vitiligo.	• Percentage change from baseline in immune biomarkers, including CXCL10, at Week 4, Week 12, and Week 24.
Secondary	
• To correlate the change in key serum and skin biomarkers of vitiligo to efficacy.	• Correlation of key skin inflammatory biomarkers of vitiligo in target lesions to efficacy readouts at Week 12 and Week 24.
• To assess the safety and local tolerability of ruxolitinib cream.	• The frequency and severity of AEs.
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, vehicle-controlled study with an open-label treatment extension period in adult participants (age ≥ 18 years) with nonsegmental vitiligo who have depigmented areas including ≥ 0.5% BSA on the face, ≥ 0.5 F-VASI, ≥ 3% BSA on nonfacial areas, and ≥ 3 T-VASI. Total body involved vitiligo area (facial and nonfacial) should not exceed 50% BSA. Approximately 60 participants will be randomized 2:1 to receive initial double-blind study treatment (ruxolitinib cream 1.5%:vehicle BID) administered BID for 24 weeks (see Figure 1). Participants will be stratified by age (≤ 40 years old and > 40 years old).

During the double-blind treatment period, participants will receive ruxolitinib cream 1.5% BID or vehicle BID for 24 weeks to be applied to depigmented areas on the face and body up to 20% T-BSA. For participants with depigmentation on > 20% BSA, the investigator will discuss with the participant which areas of vitiligo to treat and will document the areas to be treated in the eCRF. Only those areas identified for treatment at baseline should be treated during the double-blind period; participants should continue to treat depigmented areas identified for treatment at baseline even if the area begins to improve or fully repigment. Refer to Section 6.1 for full information on study drug administration and to Section 6.5 for information on dose modification and additional application guidance.

After completion of the Week 24 assessments from the double-blind treatment period, eligible participants will be offered the opportunity to continue the study in the 28-week open-label treatment extension period. Participants initially randomized to vehicle will be crossed over to active drug (ruxolitinib cream 1.5% BID), and participants initially randomized to ruxolitinib cream will continue to receive treatment with ruxolitinib cream 1.5% BID. To be eligible for the open-label treatment extension period, participants must have completed the baseline and Week 24 visit assessments, be compliant with study procedures, and not have any safety issues. During the open-label treatment extension period, participants should continue to treat depigmented areas identified for treatment at baseline even if the area begins to improve or fully repigment; additionally, if any new areas of vitiligo have appeared since baseline, the new areas can be treated during the open-label treatment extension period. The total treated area in the open-label treatment extension period should not exceed 20% BSA (facial and nonfacial).

Safety endpoints, such as nature of AEs (type, frequency, and severity), vital signs, targeted physical examination, and routine laboratory investigations, will be monitored and recorded throughout the course of this study. [redacted] Samples for translational assessments (serum, PBMCs, and skin biopsies) will be collected from participants during the study. Following the last application of ruxolitinib cream at Week 52, there will be a 30-day safety follow-up period.

4.2. Overall Study Duration

Screening is up to 42 days (~6 weeks); the double-blind, vehicle-controlled treatment period is 24 weeks; the open-label treatment extension period is 28 weeks; and safety follow-up is 30 days. Total duration is up to approximately 63 weeks (see Figure 1).

The study will begin when the first participant (or legally authorized representative) signs the study ICF. The end of the study is defined as the date of the last visit of the last participant in the study or the date that the last participant discontinued study drug and completed applicable safety follow-up assessments or is lost to follow-up.

A participant is considered to have completed the study if he/she has completed all study visits, including the safety follow-up visit. 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 or if required by regulatory agency. In the event of significant safety findings, the study will be terminated. If the study is terminated prematurely, the sponsor or designee will notify the investigators, the IRBs/IECs, and 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. Age ≥ 18 years.
2. A clinical diagnosis of nonsegmental vitiligo with depigmented areas including ≥ 0.5% BSA on the face, ≥ 0.5 F-VASI, ≥ 3% BSA on nonfacial areas, and ≥ 3 T-VASI; total body vitiligo area (facial and nonfacial) should not exceed 50% BSA.
3. At least 1 active vitiligo lesion (eg, such as confetti lesion, trichrome appearance, pinkish rim, or other evidence of inflammatory activity) at the site for skin biopsy.
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, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR postmenopausal [≥ 12 months of amenorrhea without an alternative medical cause]).

   Note: Information about specific types of acceptable contraceptive measures and duration of contraceptive use are provided in Appendix A.

6. Ability to comprehend and willingness to sign an ICF.

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 (because it is a bleaching agent, not a depigmentation treatment).

4. Concurrent conditions and history of other diseases:

   a. Any other skin disease that, in the opinion of the investigator, would interfere with the study medication application or study assessments.
   b. Active acute bacterial, fungal, or viral skin infection (eg, herpes simplex, herpes zoster, chickenpox) 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 administration of study drug 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 drug administration, 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.

      – History of thrombosis, including deep venous thrombosis and pulmonary embolism.

      – 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.
- Current and/or 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 administration schedule and study assessments.
- Committed to an institution by virtue of an order issued either by the judicial or the administrative authorities.

5. Use of any of the following treatments within the indicated washout period before baseline:
   a. 1 week: Topical drugs when used on the vitiligo areas, for example, corticosteroids, calcineurin, and phosphodiesterase type 4 inhibitors or retinoids.
   b. 4 weeks:
      - Melanocyte-stimulating agents (eg, afamelanotide).
      - Immunomodulating systemic medications (eg, corticosteroids, methotrexate, cyclosporine).
      - Any other systemic therapies that could increase the skin sensitivity to UV/visible light or impact skin pigmentation, for example, tetracyclines, methoxypsoralens.
      - Received live vaccine.

        Note: Live vaccine is prohibited during the course of the study and within 4 weeks after the EOT visit.
   c. 8 weeks: Laser or any kind of phototherapy, including tanning beds or intentional UV exposure.
   d. 5 half-lives or 12 weeks, whichever is longer: biologic agents, investigational or experimental therapy, or procedures for vitiligo. Investigational biologics should be discussed with the sponsor to determine whether a longer period of discontinuation is required.
6. Previously received JAK inhibitors, systemic or topical.
7. Investigator-determined clinically significant abnormal laboratory values at screening:
   a. Hemoglobin (< 10 g/dL).
   b. Liver function tests:
      - AST or ALT $\geq 2 \times$ ULN.
      - Alkaline phosphatase and/or bilirubin $> 1.5 \times$ ULN (isolated bilirubin $> 1.5 \times$ 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.
f. Hepatitis B virus or HCV infection: Participants who are positive for hepatitis B surface antigen or hepatitis B core antibody will be eligible if they are negative for HBV DNA; these participants should be considered for prophylactic antiviral therapy. Participants who are positive for anti-HCV antibody will be eligible if they are negative for HCV-RNA.

8. Body mass index < 17 or > 40 kg/m^2.
9. Pregnant or lactating, or considering pregnancy during the period of their study participation.
10. In the opinion of the investigator are unable or unlikely to comply with the administration schedule and study evaluations.
11. Employees of the sponsor or investigator or are otherwise dependents of them.
12. Known allergy or reaction to any component of the study formulation.
13. Live with anyone participating in any current Incyte-sponsored ruxolitinib cream study.

5.3. Lifestyle Considerations

Participants should be cautioned to avoid excessive exposure to artificial sunlight (including tanning beds, sun lamps, etc).

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).

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

5.4. Screen Failures

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

No participants will be replaced at any time during this study.

6. STUDY TREATMENT

See Appendix C for COVID-19–related guidance.

6.1. Study Treatments Administered

Table 6 presents the study treatment information.

Table 6: Study Treatment Information

	Ruxolitinib	Vehicle
Study treatment name:		
MOA:	Inhibitor of the JAK family of protein tyrosine kinases	Not applicable
Dosage formulation:	Cream	
Unit dose strength(s)/dosage level(s):	1.5%	Not applicable
Route of administration:	Topical	
Administration instructions:	A thin film is applied BID to depigmented vitiligo areas on the face and body up to 20% T-BSA.	
Packaging and labeling:	Ruxolitinib cream and vehicle 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	Not applicable

The application of study drug will be limited to ≤ 20% of the participant's T-BSA, regardless of whether the participant has depigmentation on > 20% BSA. For participants with depigmentation on > 20% BSA, the investigator will discuss with the participant at baseline (Day 1) which areas of vitiligo to treat, and the areas selected for treatment must include all areas in which skin biopsies will be performed. The site should document the area to be treated in the eCRF.

All tubes of study drug will be weighed before being dispensed. All returned tubes of study drug will also be weighed.

Study drug will be applied as a thin film BID, with applications at least 8 hours apart. Participants should remove study drug from the tube in fingertip units until all of the areas to be treated are covered by a thin film.

Participants will be instructed to document treated areas and advised to limit use to no more than 1 tube (60 g) per 3-4 days. 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 drug.

On the day of a visit, the participant should not apply their morning dose of study drug at home; instead, study drug will be applied from a new kit in the clinic during the visit, under direct supervision of the site staff. The tube will be weighed before and after application to determine the participant's dosage.

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. If any other skin products that are permitted under the study Protocol are used, participants should continue these unchanged during the study.

6.1.1. Application During the Double-Blind, Vehicle-Controlled Treatment Period

During the double-blind, vehicle-controlled treatment period (up to Week 24), participants should follow the study drug application guidance below:

- Participants should apply study drug only to depigmented vitiligo areas identified by the investigators at baseline (Day 1) up to a T-BSA (facial and nonfacial) of ≤ 20%.
- Participants should continue to treat all depigmented vitiligo areas identified for treatment at baseline even if the area begins to improve or fully repigment.
- Participants who have an expansion of existing areas of vitiligo during the course of the double-blind period may treat these areas after a visit to document the VASI and other measures of vitiligo (may be an unscheduled visit), as long as the new treated T-BSA (facial and nonfacial) does not exceed 20% BSA.
- Participants who develop new vitiligo lesions during the course of the double-blind period should not treat these areas during the double-blind period. Newly developing vitiligo lesions should be documented in the eCRF, and the VASI for these new lesions should not be calculated and combined together with the area(s) to be treated identified at baseline.

6.1.2. Application During the Open-Label Treatment Extension Period

During the open-label treatment extension period (after Week 24), participants should follow the study drug application guidance below:

- Participants should apply study drug to depigmented vitiligo areas identified by the investigators at baseline (Day 1) up to a T-BSA (facial and nonfacial) of ≤ 20%.
- Participants should continue to treat all depigmented vitiligo areas identified for treatment at baseline even if the area begins to improve or fully repigment.
- Participants who have an expansion of existing areas of vitiligo during the course of the open-label period may treat these areas after a visit to document the VASI and other measures of vitiligo (may be an unscheduled visit), as long as the new treated T-BSA (facial and nonfacial) does not exceed 20% BSA.

- Participants who develop new vitiligo lesions during the course of study may treat these areas during the open-label period after a visit to document the VASI and other measures of vitiligo (may be an unscheduled visit), as long as the new treated T-BSA (facial and nonfacial) does not exceed 20% BSA. Newly developing vitiligo lesions should be documented in the eCRF and the VASI for these new lesions should not be calculated and combined together with the area(s) to be treated identified at baseline.

6.2. Preparation, Handling, and Accountability

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

Only participants enrolled in the study may receive study drug, and only authorized site staff may supply study drug. Immediately after application of study drug, 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 drug.

All study drug 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 drug at ambient temperature conditions.

The investigator (or designee) is responsible for study treatment 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 drugs to the study site.
- Inventory of study drugs at the site.
- Participant use of the study drugs, including tube counts from each supply dispensed.
- Return of study drugs 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 drug. 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 drug 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 drug back to the sponsor or its designee for destruction according to institutional SOPs. If local procedures mandate on-site destruction of the 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 drug 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 drugs is included in the study materials provided to sites.

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to study treatment using an IRT system. The system will assign study treatment in a 2:1 ratio (ruxolitinib cream 1.5% BID:vehicle BID), stratified by age (≤ 40 years old and > 40 years old). The IRT will assign participant ID numbers, track participant visits, randomize participants according to the defined parameters, maintain the blinding, and manage study drug inventory. Full details will be provided in the IRT Manual. Study treatment will be dispensed at the study visits summarized in the SoA (see Table 3 and Table 4).

After the database lock for the primary analysis, the sponsor will be unblinded, but investigators and participants will still be blinded to individual treatment assignments. This is implemented to minimize bias for the Week 52 analyses. After Week 52, investigators and participants will be unblinded.

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 or vehicle will be evaluated by participants' adherence to the application regimen and drug accountability documented by the site staff and monitored by the sponsor/designee (tube counts).

In general, the application compliance will be determined by the number of actual versus anticipated number of applications, which should be at least 70% but no more than 130% of the prescribed number of applications. Participants will be instructed to bring all study drug with them to the study visits in order for site personnel to conduct tube counts to assess study drug accountability. The drug accountability documentation will be used by the sponsor to calculate treatment compliance.

6.5. Dose Modifications

6.5.1. Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug

Safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

In some circumstances, it may be necessary to temporarily interrupt treatment with study drug. 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's medical monitor (or other representative of the sponsor) before interrupting study drug. Additionally, the investigator must obtain approval from the sponsor before restarting study drug. Participants who experience a

recurrence of the initial AEs upon restarting the study drug may need the study drug to be permanently discontinued.

Instructions for application interruptions of study drug are outlined in Table 7. 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 treatment and the participant's underlying condition.

Table 7: Guidelines for Interruption and Restarting of Study Drug

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 drug applications must be interrupted. At the discretion of the investigator, after consultation with the sponsor, study drug application may be restored once these have resolved.
Other laboratory abnormalities	
Any other Grade 3 laboratory abnormality, with the exception of asymptomatic elevations in triglyceride, cholesterol, or amylase	• Laboratory abnormalities should be confirmed with repeat testing within 48 hours whenever possible and immediate delivery of the laboratory results requested. • Study drug applications must be interrupted. At the discretion of the investigator, after consultation with the sponsor, study drug 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 drug if laboratory abnormalities are confirmed.

6.5.2. Criteria for Permanent Discontinuation of Study Drug

The occurrence of unacceptable severity of an AE not caused by the underlying disease will be presumed to be related to study drug and will require that the study drug be permanently discontinued. Unacceptable severity is defined as follows:

- Occurrence of an AE that is related to treatment with the study drug 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 to not be in the participant's best interest.
- Worsening of vitiligo that requires treatment with a prohibited concomitant medication.

See Section 7 for discontinuation procedures.

6.6. 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 prior medication received up to 42 days before the first dose of study drug through 30 days after the last dose of study drug will be recorded in the eCRF. Any addition, deletion, or change in the dose of these medications will also be recorded. Concomitant medications administered after 30 days after the last dose of study drug should be recorded in the eCRF only if the medication was administered due to an SAE (as defined in Section 9.2). Concomitant treatments/procedures that are required to manage a participant's medical condition during the study will also be recorded in the eCRF. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

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 drug application. The study drug may not be applied over sunscreens and camouflage makeup. These must be carefully removed from the skin before application of the study drug. Any makeup remover must then be washed off and the skin dried before application of the study drug.

- If sunscreen is needed, a mineral-based sunscreen (such as zinc oxide– or titanium oxide–based) with SPF of at least 30 may be used at least 2 hours after study drug application.

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

- Study drug should be applied at least 2 hours after shaving.
- 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 Procedures

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 drug application.
- Treatment for dermatologic disease besides vitiligo (eg, atopic dermatitis 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 B) are at a stable dose.
  - Topical corticosteroids Class 1 through 5 (see Appendix B) 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).

6.6.3. 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 drug
- 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) 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)
- Biologic therapies or other immunosuppressant agents
- Any phototherapy, including tanning beds
- Live or live-attenuated vaccination

6.7. Treatment After the End of the Study

No treatment will be provided after the end of the 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:

- A participant is found not to have met eligibility criteria (any exclusion criterion or any inclusion criterion related to participant safety) or if legal requirements have been violated.
- The participant becomes pregnant.
- Consent is withdrawn.

  Note: Consent withdrawn means that the participant has explicitly indicated that he/she does not want to be followed any longer; in this case no further data, except data in the public domain, may be solicited from or collected on the participant. Participants may choose to discontinue study treatment and remain in the study for safety monitoring.
- 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:

- If, at 2 consecutive study visits, a participant's drug usage exceeds 1 tube (60 g) per 3-4 days.
- If a participant is noncompliant with study procedures or study drug administration 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 study treatment, an EOT visit should be conducted (EOT1 or EOT2, depending on the period during with the participant discontinues treatment). Reasonable efforts should be made to have the participant return for a safety follow-up visit. These visits are described in Table 3 and Table 4. The last date of the last dose of study drug and the reason for discontinuation of study drug 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 discontinuation must be documented in the participant's medical record and the primary reason for discontinuation must be included in the eCRF.

- An EOT visit should be performed (EOT1 or EOT2, depending on the period during with the participant discontinues treatment).
- 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 treatment–related AEs resolve, return to baseline, or are deemed irreversible, whichever is longest.

If the participant discontinues study treatment 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 of the study for safety [redacted] assessments.

7.2. Participant Withdrawal From the Study

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

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

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.

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 site will counsel the participant on the importance of maintaining the assigned visit schedule and will 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, he/she 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 his/her representative will explain the nature of the study to the participant or his/her 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.
  - 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 country in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that his/her 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 his/her 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.
- Participants who are rescreened are required to sign a new ICF.

8.1.2. Screening Procedures

Screening is the interval between signing the ICF and the day that the participant is assigned to the study drug (Day 1). Screening assessments for determination of eligibility may be performed over a period lasting up to 42 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 42 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 administration of study drug. Test 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 recently available result before administration of study drug will be used to determine eligibility. See Section 5.4 regarding screen failures.

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 site ID and 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 drug supply. Additional details are provided in the IRT Manual.

8.1.4. Distribution of Reminder Cards and Diaries

Starting at the baseline (Day 1) visit and each visit thereafter (except for the Week 24 [EOT1], Week 52 [EOT2], and EOS visits), a study drug–specific diary will be given to each participant in order to record use of the study drug. 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 drug schedule (defined as < 70% or > 130% of the expected number of applications between study visits) will have their administration 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 52). The reminder card will indicate the date/time of the next visit and will also remind the participant that on visit days, they will perform their morning study drug application at the clinic during the visit under site supervision after their blood draws for [redacted] 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 past 2 years that are considered to be clinically significant by the investigator.

8.1.5.2. Disease Characteristics and Treatment History

A 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. A medical history of other conditions related to vitiligo will also be collected at screening.

[redacted]

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 dose of study drug. Adverse events for randomized 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 drug. 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 drug, or that caused the participant to discontinue the study drug. 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 be conducted as indicated by symptoms reported by the participant, AEs, or other findings.

Physical examinations must be performed by a medically qualified individual such as a licensed physician, a physician assistant, or an advanced registered nurse practitioner, as local law permits. Abnormalities identified after the first dose of study drug constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment.

8.3.3. Vital Signs

Vital sign measurements will be taken at all visits.

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 as indicated in Table 3.

All 12-lead ECGs will be performed with the participant in a recumbent or semirecumbent position after 5 minutes of rest. Additional 12-lead ECGs may be performed at other visits as deemed clinically necessary. Findings from a 12-lead ECG performed within 2 months before baseline are acceptable to use as the participant's screening value.

ECGs will be interpreted by the investigator at the site or designee, and the results will be used for immediate management of the participant's care. There is no central reader of ECGs for this study. The decision to include or exclude a participant or withdraw a participant from the study 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. Any abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

8.3.5. Laboratory Assessments

Required clinical laboratory tests are listed in Table 8, which include hematology, chemistry, urinalysis, serology, free T4, TSH, FSH, and pregnancy testing, and will be performed as indicated in Table 3 and Table 4. 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 are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. All laboratory tests with values considered clinically significantly abnormal during participation in the study, or within 30 days after the last dose of study drug, 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 8: Required Laboratory Analytes

<table>
<tr><th>Serum Chemistries[a]</th><th>Hematology</th><th>Urinalysis With Microscopic Examination</th><th>Serology</th><th>Other</th></tr>
<tr><td rowspan="2">Albumin
Alkaline phosphatase
ALT
AST
Bicarbonate or CO_2
Blood urea nitrogen or urea
Calcium
Chloride
Creatinine
Glucose
Lactate dehydrogenase
Phosphate
Potassium
Sodium
Total bilirubin
Direct bilirubin (if total bilirubin is elevated above ULN)
Total protein</td><td rowspan="2">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</td><td>Hepatitis B surface antigen
Hepatitis B core antibody
Hepatitis B core immunoglobulin M antibody
HCV antibody
HCV-RNA (only performed if antibody positive)
HIV antibody</td><td>FSH[b]
Free T4
TSH</td></tr>
<tr><td colspan="3">Pregnancy Testing
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 upon by the 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; EOT1 or EOT2 as applicable). 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 drug 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

Hepatitis and HIV screening assessments will be performed during the screening period to rule out infection; required analytes are shown in Table 8.

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.

[redacted]

8.5. Pharmacodynamic and Translational Assessments

All participants will have serum, [redacted] and 2.5-mm skin biopsies collected at the visits outlined in Table 3. Serum [redacted] will be used for changes in immune parameters, including but not limited to soluble proteins, such as cytokines and chemokines, [redacted]. [redacted]

[redacted]

All analyses will be conducted by Incyte Corporation (Wilmington, DE) or Incyte's designee. Refer to the procedure-specific Study Manuals for detailed instructions.

8.5.1. Skin Biopsy

Skin biopsies (2.5 mm punch biopsy) will be collected from a target lesion at the timepoints outlined in Table 3. Skin biopsies cannot be taken from the hands, feet, head/neck, face, and genital area. The target lesion for skin biopsy should be defined at baseline (Day 1) as an active vitiligo lesion, such as confetti lesion, trichrome appearance, pinkish rim, or other evidence of inflammatory activity and/or active changes to the lesion.

[redacted] small (2.5 mm, which does not require stitches) biopsies will be collected from lesional skin at each timepoint (Baseline/Day 1, Week 12, Week 24, and Week 40) [redacted]. At baseline (Day 1), an additional [redacted] small (2.5 mm) skin biopsies will also be collected from nonlesional skin adjacent to the target lesion, [redacted]. [redacted] small biopsies will be taken at each timepoint to accommodate different analyses, each requiring profoundly different processing. At each timepoint, 1 biopsy will be processed for immunohistochemistry and other imaging technologies to enable protein and gene expression analyses by imaging, [redacted]

The skin biopsies at Week 12, Week 24, and Week 40 will be collected in the vicinity but at least 1 cm distant from where the biopsies were collected at baseline (Day 1), even if the target lesion area has cleared. The baseline (Day 1) lesional skin biopsy sampling area should be from the inside edge of an active vitiligo lesion, and the sampling area should be entirely contained within lesional skin.

Details about the collection, processing, handling, storage, and shipping of samples will be provided in the Study Manuals.

[redacted]

[redacted]

8.5.3. Immunohistology and Other Imaging Techniques

Analyses will be performed [redacted] to evaluate skin [redacted] biomarkers. This will enable, but not limit, the evaluation of changes in leukocyte infiltration to vitiligo lesions and the correlation with biological response relating to vitiligo or the MOA of ruxolitinib 1.5% cream.

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 study drug, then an EOT visit should be conducted (EOT1 or EOT2, depending on the study period when the participant discontinues). 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 (EOT1 or EOT2, depending on the study period when the participant discontinues) and the scheduled safety follow-up visit, which should occur 30 (+ 7) days after the EOT visit (or after the last dose of study drug if an EOT visit was not performed).

Adverse events and SAEs must be reported up until 1) at least 30 days after the last dose of study drug or the date of the safety follow-up visit or 2) until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. 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 drug.
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 drug. 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 drug administration 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 dosing errors of a study drug (eg, overdose) or a concomitant medication are to be reported as an AE. • [redacted] "disease progression," or "failure of expected pharmacological action" will not be reported as an AE or SAE. [redacted]. • 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. If the condition is 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, convulsions that do not result in hospitalization, development of drug dependency or drug abuse, or suspected transmission of an infectious agent via a medicinal product.

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 randomized participants, but only SAEs need to be reported for screen failure participants. For randomized 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 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 drug: 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 drug 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 drug 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 for study drug in making his/her 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 drug administration, will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she 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 his/her 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 drug, 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 (either via email/fax if paper SAE form is used or in the SAE EDC CRF) 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 drug or study procedure[s]), all SAEs occurring after the participant has signed the ICF through the last study visit (or 30 days after the last dose of study drug, whichever occurs later) must be reported to the sponsor (or designee) immediately, without undue delay, under no circumstances later than **24 hours** following knowledge of the event.

Investigators are not obligated to actively seek AE or SAE information after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers it is at least reasonably possible that the event is related to the study drug or study participation, then the investigator must notify the sponsor (or designee) immediately, without undue delay, under no circumstances later than 24 hours following knowledge 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 of a SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study drug under clinical investigation are met.

If the SAE is not documented in the RSI of the IB for the study drug (new occurrence) and is thought to be related to the study drug, the sponsor or its designee may urgently require further information from the investigator for 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 drug 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 also complete the Incyte Serious Adverse Event Report Form in English. • Follow-up information is also recorded and transmitted to Incyte Pharmacovigilance on an amended or new Serious Adverse Event Report Form, with an indication that it is follow-up to the previously reported SAE and the date of the original report. The follow-up report should include information that was not provided on the previous Serious Adverse Event Report Form, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with study drug because of the SAE (eg, dose 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. • Contacts for SAE reporting can be found in the Study Manual.

9.5. Events of Clinical Interest

Not applicable.

9.5.1. Adverse Events of Special Interest

Not applicable.

9.6. Emergency Unblinding of Treatment Assignment

In a medical emergency during the double-blind, vehicle-controlled period, if the investigator deems it necessary to determine optimal medical management of the participant, emergency unblinding will be performed exclusively by the principal investigator and subinvestigator as described in the IRT Study Manual. The IRT system has an option to select for "Emergency Code Break" action for a given participant. After entering the 6-digit study drug tube number and verification of the unmasking information, the investigator/subinvestigator will proceed to either final confirmation or cancellation of the code break procedure.

If a participant's treatment assignment is unblinded, the sponsor or its designee must be notified immediately by telephone, followed up with an email.

If an investigator, site personnel performing assessments, or participant is unblinded, the participant must discontinue study drug unless there are ethical reasons to have the participant remain on the study drug. In these cases, the investigator must obtain specific approval from the sponsor's (or its designee's) medical monitor for the participant to continue in the study.

9.7. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that the study drug 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 drug, the following procedures should be followed in order to ensure safety:

- The study drug 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 drug 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.

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 drug, 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 drugs 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 his/her 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, he/she 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.

10. STATISTICS

10.1. Sample Size Determination

Due to the exploratory nature of the study, the sample size is not only based on calculation of statistical power. The sample size is considered to be sufficient to obtain adequate [redacted] safety, tolerability, [redacted] data to achieve the objectives of the study.

Approximately 60 participants will be randomized 2:1 to ruxolitinib cream 1.5% BID or vehicle BID to ensure approximately 45 participants will have multiple biomarker data (eg, CXCL10) available at Week 24.

On the basis of the results of a Phase 2 study (INCB 18424-211), the anticipated difference in percentage of change from baseline in CXCL10 between ruxolitinib cream 1.5% BID and vehicle is 22% (standard deviation = 0.25%). Using a 2-sample t-test, the sample size of 45 will provide great power (≥ 80%) to detect such difference with a 2-sided alpha of 0.10.

10.2. Populations for Analysis

The populations for analysis are provided in Table 9.

Table 9: Populations for Analysis

Population	Description
ITT	The ITT population includes all randomized participants. Treatment groups for this population will be defined according to the treatment assignment at randomization.
Safety	The safety population includes all participants who applied at least 1 dose of study drug. Treatment groups for this population will be determined according to the actual treatment the participant received on Day 1.
[redacted]	

10.3. Level of Significance

Not applicable.

10.4. Data Handling Definitions and Conventions

10.4.1. Day 1

Day 1 is the date that the first application of ruxolitinib cream or vehicle cream is administered to the participants.

For randomized participants not treated with any study drug, Day 1 is defined as the day of randomization.

10.4.2. Study Day

If a visit/reporting date is on or after Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (Visit/Reporting Date – Day 1 date + 1).

If the visit/reporting date is before Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (Visit/Reporting Date – Day 1 date).

A study day of −1 indicates 1 day before Day 1.

10.4.3. Baseline Value

Baseline is the last nonmissing measurement obtained before or on the day of first application of ruxolitinib cream or vehicle cream.

For randomized participants not treated with any study drug, baseline is defined as the last nonmissing assessment before or on the day of randomization for all parameters.

10.4.4. Handling of Missing and Incomplete Data

In general, missing data will not be imputed.

10.5. Statistical Analyses

10.5.1. Baseline, Demographics, Disease History, and Prior and Concomitant Medication

The following demographics will be summarized for the ITT population: age, age group, sex, race, ethnicity, region, weight, height, and body mass index.

Baseline disease characteristics, prior medications for vitiligo, medical history, and prior and concomitant medications will be summarized by treatment group.

10.5.2. Disposition of Participants

The number and percentage of participants who were enrolled, randomized, treated, and completed for each period will be summarized for the ITT population.

10.5.3. Exposure and Study Drug Compliance

For participants in the ITT population, descriptive statistics will be provided for duration of treatment, average daily dose, total dose, and study drug compliance.

[redacted]

10.5.5. 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 10.

Table 10: Safety Analyses

Objective	Statistical Analysis Methods
To assess the safety and local tolerability of ruxolitinib cream.	**Adverse Events** A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study drug administration. 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 drug will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study drug, 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. The following summaries will be produced for the laboratory data: • Number and percentage of participants with worst postbaseline CTCAE grade (regardless of baseline value). Each participant will be counted only for the worst grade observed postbaseline. • Shift tables from baseline to the worst postbaseline value using CTCAE grade. • For laboratory parameters where CTCAE grades are not defined, shift tables to the worst postbaseline value using the low/normal/high classifications based on laboratory reference ranges. **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. **Electrocardiograms** Descriptive statistics and mean change from baseline will be determined for each ECG parameter at each assessment time.

10.5.6. Translational Analyses

Translational endpoints are listed in Section 3. These are being evaluated as primary, secondary, [redacted] objectives. Details of translational analyses will be provided in the Statistical Analysis Plan.

[redacted]

10.6. Interim Analysis

No formal interim analysis is planned in this study. The primary analysis will occur after the primary database lock, when all participants have completed the vehicle-controlled, double-blind treatment period. The sponsor will be unblinded, while investigators and participants will still be blinded, to the study treatment after the primary database lock. After Week 52, investigators and participants will be unblinded.

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 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.

11.2. 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 biomarker plans, 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, biomarker data, 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 (e.g., 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 (e.g., 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.

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 his/her 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.

12. REFERENCES

Clinical Trials Facilitation and Coordination Group. Recommendations related to contraception and pregnancy testing in clinical trials. 2014.

Dina Y, McKesey J, Pandya AG. Disorders of hypopigmentation. J Drugs Dermatol 2019;18:s115-s116.

European Medicines Agency. Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic. 2020.

González U, Whitton M, Eleftheriadou V, Pinart M, Batchelor J, Leonardi-Bee J. Guidelines for designing and reporting clinical trials in vitiligo. Arch Dermatol 2011;147:1428-1436.

[redacted]

Howell MD, Kuo FI, Smith PA. Targeting the Janus kinase family in autoimmune skin diseases. Front Immunol 2019;10:2342.

Krüger C, Schallreuter KU. A review of the worldwide prevalence of vitiligo in children/adolescents and adults. Int J Dermatol 2012;51:1206-1212.

Rashighi M, Agarwal P, Richmond JM, et al. CXCL10 is critical for the progression and maintenance of depigmentation in a mouse model of vitiligo. Sci Transl Med 2014;6:223ra23.

Rashighi M, Harris JE. Interfering with the IFN-γ/CXCL10 pathway to develop new targeted treatments for vitiligo. Ann Transl Med 2015;3:343.

Rosmarin D, Pandya AG, Lebwohl M, et al. Ruxolitinib cream for treatment of vitiligo: a randomised, controlled, phase 2 trial. Lancet 2020;396:110-120.

Ruxolitinib Cream Investigator's Brochure. Wilmington, DE: Incyte Corporation.

Taïeb A, Picardo M. Clinical practice. Vitiligo. N Engl J Med 2009;360:160-169.

van den Boorn JG, Konijnenberg D, Dellemijn TA, et al. Autoimmune destruction of skin melanocytes by perilesional T cells from vitiligo patients. J Invest Dermatol 2009;129:2220-2232.

World Health Organization. WHO Model Prescribing Information: Drugs Used in Skin Diseases. 1997.

APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS AND DEFINITIONS

For male participants in the study:

Male participants should use a condom during treatment through 90 days after the end of systemic exposure. If the male participant has a partner that is of childbearing potential, the partner should also use contraception through 90 days after the end of relevant systemic exposure. In addition, male participants must refrain from donating sperm during the study through 90 days after the end of relevant systemic exposure. Male participants who have had a vasectomy qualify as having met the requirement for a highly effective birth control method.

For female participants in the study:

The following methods that can achieve a failure rate of < 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
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - oral
  - injectable
  - implantable[a]
- Intrauterine device[a]
- Intrauterine hormone-releasing system[a]
- Bilateral tubal occlusion[a]
- Vasectomized partner[ab]
- Sexual abstinence[c]

Acceptable birth control methods that result in a failure rate of more than 1% per year include:[d]

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide[e]
- Cap, diaphragm, or sponge with spermicide[e]
- Tubal ligation

[a] Contraception methods that in the context of this guidance are considered to have low user dependency.

[b] Vasectomized partner is a highly effective method of avoiding pregnancy provided that the partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of the surgical success.

[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] Choices are for US and Canada participants only and include above < 1% failure rate methods.

[e] Combinations of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

Source: Clinical Trials Facilitation and Coordination Group 2014.

APPENDIX B. 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.

[redacted]

APPENDIX D. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Not applicable.

Signature Page for VV-CLIN-011898 v3.0

Approval	[redacted] Approver 03-Mar-2021 17:02:15 GMT+0000

Approval	[redacted] Approver 03-Mar-2021 17:08:12 GMT+0000

Approval	[redacted] Approver 03-Mar-2021 17:14:13 GMT+0000

Approval	[redacted] Approver 03-Mar-2021 17:19:42 GMT+0000

Approval	[redacted] Approver 03-Mar-2021 19:00:43 GMT+0000

Signature Page for VV-CLIN-011898 v3.0