Official Title: A Double-Blind, Vehicle-Controlled, Randomized Withdrawal and Treatment Extension Study to Assess the Long-Term Efficacy and Safety of Ruxolitinib Cream in Participants With Vitiligo (TRuE-V LTE)

NCT Number: NCT04530344

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Clinical Study Protocol

INCB 18424-308

A Double-Blind, Vehicle-Controlled, Randomized Withdrawal and Treatment Extension Study to Assess the Long-Term Efficacy and Safety of Ruxolitinib Cream in Participants With Vitiligo (TRuE-V LTE)

Product:	**Ruxolitinib Cream**
IND Number:	[redacted]
EudraCT Number:	**2020-000987-53**
Phase of Study:	**3**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol:	**19 MAR 2020**
Protocol Amendment 1:	**28 SEP 2020**
Protocol Amendment 2:	**10 NOV 2020**

INVESTIGATOR'S AGREEMENT

I have read the INCB 18424-308 Protocol (Amendment 2 dated 10 NOV 2020) 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
2D	2-dimensional
3D	3-dimensional
AD	atopic dermatitis
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice daily
BSA	body surface area
CDC	Centers for Disease Control and Prevention
CDLQI	Children's Dermatology Life Quality Index
CFR	Code of Federal Regulations
CO_2	carbon dioxide
COVID-19	coronavirus disease 2019
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment
FAS	Full Analysis Set
F-BSA	facial body surface area
[redacted]	
F-VASI	Face Vitiligo Area Scoring Index
F-VASI50/75/90	≥ 50%/ 75%/ 90% improvement from baseline in Face Vitiligo Area Scoring Index score
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	identification

Abbreviations and Special Terms	Definition
IEC	independent ethics committee
INFO	International Initiative for Outcomes for Vitiligo
IRB	institutional review board
IRT	interactive response technology
ITT-Ext	intent to treat long-term extension
JAK	Janus kinase
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NB-UVB	narrowband ultraviolet B
[redacted]	[redacted]
PASI	Psoriasis Area and Severity Index
PD	pharmacodynamic
PDCO	Paediatric Committee
[redacted]	[redacted]
PhV	pharmacovigilance
PK	pharmacokinetic
PUVA	psoralen and ultraviolet A
QD	once daily
Rux	ruxolitinib
SAE	serious adverse event
SoA	schedule of activities
SOP	standard operating procedure
SPF	sun protection factor
SUSAR	suspected unexpected adverse reaction
T-BSA	total body surface area
TEAE	treatment-emergent adverse event
[redacted]	
T-VASI	total body Vitiligo Area Scoring Index
T-VASI50/75/90	≥ 50%/ 75%/ 90% improvement in total body Vitiligo Area Scoring Index
TYK	tyrosine kinase
ULN	upper limit of normal
US	United States (of America)
UV	ultraviolet
VASI	Vitiligo Area Scoring Index
[redacted]	
VNS	Vitiligo Noticeability Scale
WHO	World Health Organization
[redacted]	

1. PROTOCOL SUMMARY

Protocol Title: A Double-Blind, Vehicle-Controlled, Randomized Withdrawal and Treatment Extension Study to Assess the Long-Term Efficacy and Safety of Ruxolitinib Cream in Participants With Vitiligo (TRuE-V LTE)

Protocol Number: INCB 18424-308

Objectives and Endpoints:

Table 1 presents the primary and secondary endpoints and objectives.

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the duration of clinical response of ruxolitinib cream in participants with vitiligo.	For participants who are randomized in Cohort A: • Time to relapse (defined as < F-VASI75).
Key Secondary	
To evaluate the duration of clinical response of ruxolitinib cream in participants with vitiligo.	For participants who are randomized in Cohort A: • Time to maintain ≥ F-VASI90 response.
Secondary	
To further evaluate the efficacy of ruxolitinib cream.	• Proportion of participants who achieve F-VASI50/75/90 during the extension treatment period. • Actual measurements, change, and percentage change from baseline in F-VASI. • Proportion of participants who achieve T-VASI50/75/90 during the extension treatment period. • Actual measurements, change, and percentage change from baseline in T-VASI. • Actual measurements, change, and percentage change from baseline in F-BSA. • Actual measurements, change, and percentage change from baseline in T-BSA. • Proportion of participants achieving a VNS of "4 – A lot less noticeable" or "5 – No longer noticeable" during the extension treatment period.
To determine the participants' quality of life.	• Change from Week 52 in DLQI (or CDLQI) during the extension treatment period.
To evaluate the safety and tolerability of ruxolitinib cream.	• The frequency and severity of AEs; includes performing physical examinations and collecting vital signs and laboratory data for hematology and serum chemistry.
To evaluate the ruxolitinib PK in plasma after treatment with ruxolitinib cream.	• Trough plasma concentrations of ruxolitinib at Week 80 and Week 104.

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 3
Clinical Indication	Vitiligo
Population	Male and female participants from Study INCB 18424-306 or Study INCB 18424-307 (parent studies) conducted in adults and adolescents with vitiligo who adequately completed the visits and assessments required for the treatment periods, as defined in the parent study protocol, and tolerated ruxolitinib cream treatment without safety concern for continuation.
Number of Participants	Approximately 500
Study Design	Double-blind, vehicle-controlled, randomized withdrawal (Cohort A) and treatment extension (Cohort A and Cohort B)
Estimated Duration of Study Participation	Extension treatment period: 52 weeks Safety follow-up: 4 weeks (30 days) after last application of study treatment or last study visit Total: Up to approximately 56 weeks
DSMB	No

Treatment Groups and Duration:

This is a Phase 3, double-blind, vehicle-controlled, randomized withdrawal and treatment extension study that will enroll eligible participants who have completed either Study INCB 18424-306 or Study INCB 18424-307 (parent studies) in which the participants will have been using ruxolitinib cream 1.5% BID for the previous 28 to 52 weeks (depending on their initial randomization in the parent study; see Figure 1). Participants who successfully complete either of the parent studies and tolerated ruxolitinib treatment without safety concern and with good compliance for continuation may be eligible to participate in this treatment extension study.

The parent study population comprised adolescent and adult participants (age ≥ 12 years) with non-segmental vitiligo who had depigmented area including ≥ 0.5% BSA on the face, ≥ 0.5 F-VASI, ≥ 3% BSA on nonfacial areas, and ≥ 3 T-VASI, with total body involved vitiligo area (facial and nonfacial) that was not to exceed 10% BSA.

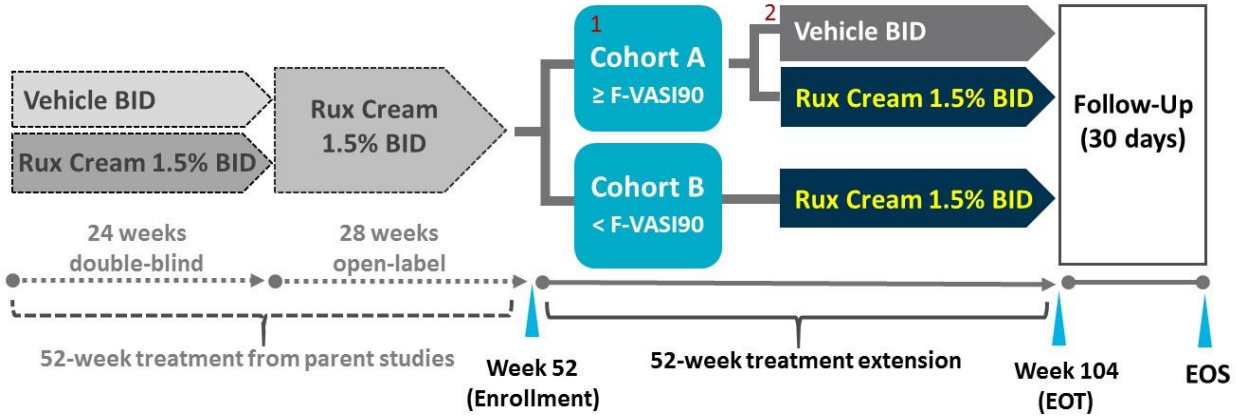
Eligible participants in this treatment extension study will be assigned to one of 2 cohorts, Cohort A or Cohort B, based on their F-VASI responses at the time of enrollment in this extension study (ie, at Week 52). Participants who achieve complete or almost complete facial repigmentation (ie, achieve ≥ F-VASI90) at Week 52 in the parent study will be assigned to Cohort A, stratified by the original treatment received on study Day 1 of the parent study, and randomized 1:1 to treatment with vehicle cream BID or ruxolitinib cream 1.5% BID for an additional 52 weeks (ie, until EOT at Week 104). However, any participants in Cohort A who experience relapse (defined as < F-VASI75) will receive ruxolitinib cream 1.5% BID as an open-label rescue treatment until they complete treatment (Week 104 or EOT). Participants who did not achieve ≥ F-VASI90 at Week 52 of the parent studies will be assigned to Cohort B and

will continue ruxolitinib cream 1.5% BID for 52 weeks (ie, until EOT at Week 104). For Cohort A, the participant, investigator, and sponsor will remain blinded to treatment assignment; the treatment for Cohort B will be open-label.

See Section 4.1 for full details of the study design.

Figure 1 presents the study design schema, and Table 3 presents the SoA. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Figure 1: Study Design Schema



1. All participants in Cohort A will use their randomly assigned treatment (either vehicle or ruxolitinib cream) on both the face and total body.
2. Rescue treatment: If, at any time, a participant in Cohort A loses a clinically meaningful response on the face (< F-VASI75), the participant will receive open-label 1.5% BID ruxolitinib cream until Week 104 or EOT.

Table 3: Schedule of Activities

Evaluation	Parent Study	Extension Treatment Period						Safety Follow-Up	Notes
	Week 52 (Parent Study) ± 7 d	Enrollment (Week 52) ± 7 d[a]	Weeks 56, 60, and 64 ± 7 d	Week 68[b] ± 7 d	Week 80[b] ± 7 d	Week 92[b] ± 7 d	Week 104[b] (EOT) ± 7 d	30 Days After EOT (EOS) + 7 d	
Administrative procedures									
Informed consent		X							
Inclusion and exclusion criteria		X							
Contact IRT		X	X	X	X	X	X	X	
Concomitant medications	X		X	X	X	X	X	X	
Apply study drug		X	X	X	X	X			
Dispense (D) and return (R) study drug and diary cards	R	D	R/D	R/D	R/D	R/D	R		
Safety assessments									
AE assessment	X	X	X	X	X	X	X	X	
Comprehensive physical examination	X						X		
Targeted physical examination				X	X	X		X	A targeted physical examination should be conducted as indicated by symptoms reported by the participant, AEs, or other findings. Abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs. See Section 8.3.2.
Vital signs	X		X	X	X	X	X	X	
Efficacy assessments									
F-BSA	X		X	X	X	X	X	X	
T-BSA	X		X	X	X	X	X	X	Includes facial and nonfacial areas.
F-VASI	X		X	X	X	X	X	X	
T-VASI	X		X	X	X	X	X	X	Includes facial and nonfacial areas.
[redacted]									

Table 3: Schedule of Activities (Continued)

Evaluation	Parent Study	Extension Treatment Period						Safety Follow-Up	Notes
	Week 52 (Parent Study) ± 7 d	Enrollment (Week 52) ± 7 d[a]	Weeks 56, 60, and 64 ± 7 d	Week 68[b] ± 7 d	Week 80[b] ± 7 d	Week 92[b] ± 7 d	Week 104[b] (EOT) ± 7 d	30 Days After EOT (EOS) + 7 d	
Efficacy assessments (continued)									
Photography of face	X			X	X	X	X	X	2D photograph at all sites; 3D photography at selected sites.
Photography of nonfacial target area	X			X	X	X	X	X	2D photography at all sites. The genitalia area should not be photographed.
Patient-reported outcomes									To be evaluated prior to any other study procedures/assessments.
VNS	X		X	X	X	X	X	X	The participant will be provided their baseline photo and a mirror to perform this assessment.
[redacted]									
DLQI	X		X	X	X	X	X	X	For participants who are age < 16 years at baseline (Day 1) of the parent study, the CDLQI will be completed instead.
[redacted]									

Table 3: Schedule of Activities (Continued)

Evaluation	Parent Study	Extension Treatment Period						Safety Follow-Up	Notes
	Week 52 (Parent Study) ± 7 d	Enrollment (Week 52) ± 7 d[a]	Weeks 56, 60, and 64 ± 7 d	Week 68[b] ± 7 d	Week 80[b] ± 7 d	Week 92[b] ± 7 d	Week 104[b] (EOT) ± 7 d	30 Days After EOT (EOS) + 7 d	
Laboratory assessments									
Hematology and chemistry assessments	X		X	X	X	X	X	X	
Pregnancy testing	X*		X	X	X	X	X	X*	*Female participants of childbearing potential will have a serum pregnancy test at Week 52 and at the safety follow-up visit. A urine pregnancy test will be conducted at all other visits. A positive urine test must be confirmed by a serum test.
PK [redacted] assessments									
PK plasma sampling (trough)					X*		X		Time of last study drug application to be recorded in eCRF. Blood samples must not be drawn from the area that has been treated with study drug. *Samples will be drawn at predose.
[redacted]									

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

[a] All scheduled assessments for the Week 52 visit must be performed before participants who meet eligibility criteria may enter the extension treatment period of this study.

[b] Starting from Week 68, participants will be contacted by site personnel via telephone call every 4 weeks until Week 104 to follow-up on disease status. If there is any disease progression or any concerns, unscheduled visits may occur.

2. INTRODUCTION

Ruxolitinib cream is in Phase 3 development for the treatment of vitiligo and is a topical formulation of ruxolitinib phosphate, an inhibitor of the JAK family of protein TYKs. Because JAKs serve to translate extracellular signals from a number of relevant cytokines and growth factors upregulated in inflammatory diseases such as vitiligo, JAK inhibitors represent potential therapeutic agents for this condition.

2.1. Background

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

Vitiligo is considered a serious disease owing to its substantial psychological burden on patients and its progressive course if left untreated. Involvement of exposed skin (eg, face and hands) can have a major negative impact on self-esteem and quality of life (Silverberg and Silverberg 2013). Studies also suggest that the onset of vitiligo beginning in childhood can be associated with significant psychological trauma that may have long lasting effects on self-esteem (Linthorst Homan et al 2008). A majority of vitiligo sufferers feel their appearance is moderately to severely intolerable, are distressed about their disease, experience stigmatization, and have feelings of anxiety and embarrassment when meeting strangers or beginning a new sexual relationship (Porter et al 1990, Salzer and Schallreuter 1995, Krüger et al 2014). Additionally, based on various meta-analyses, patients with vitiligo are approximately 5 times more likely to suffer from depression than healthy controls (Lai et al 2017, Wang et al 2018, Osinubi et al 2018).

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

No available product or therapy is able to modify the course of vitiligo disease and produce a long-lasting effect. Given the lack of approved therapies and safety concerns and modest

effectiveness of current off-label drug treatments, there is a need to identify a safe and effective new treatment for vitiligo.

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

2.1.1. Preclinical Safety

In preclinical studies, ruxolitinib cream did not act as a contact sensitizer nor did it produce significant dermal irritation or demonstrate phototoxicity or photoallergenic potential. Topical application of ruxolitinib cream 1.5% QD for 9 months to Gottingen minipigs did not result in any adverse systemic effects.

The toxicity of ruxolitinib has been evaluated following oral administration to mice, rats, and dogs. Findings in these studies were primarily those associated with the mechanism of action of ruxolitinib, including decreases in red blood cells, reticulocytes, eosinophils, and lymphocytes, which have been observed along with lymphoid depletion in bone marrow and lymphoid organs. Systemic exposures in these studies exceeded those anticipated with topical application. Ruxolitinib was not teratogenic when administered to pregnant rats or rabbits; there were no adverse developmental effects at doses below those associated with maternal toxicity. In vitro testing also showed that ruxolitinib was not mutagenic or clastogenic.

In a toxicity study of orally-administered ruxolitinib in juvenile rats beginning on Days 7, 14, or 21 postpartum, dose-related effects on body weight gain and decrements in various bone measures were observed in all cohorts. Hematology and other microscopic findings were similar to those previously observed in general toxicology studies. Other than the bone findings, there were no other novel toxicities in juvenile animals. In animals administered ruxolitinib orally beginning on Day 21 postpartum (considered approximately equivalent to a 2-year-old human), bone findings occurred at exposures higher than those anticipated with topical application. The clinical relevance of these findings to humans is not clear.

Further information on preclinical toxicology and safety is summarized in ruxolitinib cream IB Sections 4.3 and 4.4.

2.1.2. Clinical Pharmacokinetics

Clinical PK studies have demonstrated that exposures of ruxolitinib were generally strength-dependent with a moderate interparticipant variability. The systemic PK following topical application in treatment of plaque psoriasis (Study INCB 18424-202) and AD (Study INCB 18424-206) is characterized by apparent first-order release, modest peak-to-trough excursion (ratio ~2), estimated relative bioavailability of 3% to 5%, and an apparent terminal elimination half-life of approximately 3 days. The plasma metabolite profile following topical application is generally similar to that observed following oral administration.

Preliminary PK data are available from topical application in treatment of vitiligo (Study INCB 18424-211). Plasma ruxolitinib concentrations reached steady-state at or before Week 4 and were similar at Week 24/Week 28 after treatment of ruxolitinib cream. Plasma concentrations of ruxolitinib for predose and 2.0-hour postdose were similar, indicating a slow rate of absorption. Application of ruxolitinib cream 0.15% QD, 0.5% QD, 1.5% QD, and 1.5% BID resulted in mean (range) plasma concentrations of 5.75 nM (0-28.8 nM), 12.6 nM (0-82.1 nM), 59.1 nM (0-245 nM), and 113 nM (0-662 nM), respectively, after 24 weeks of treatment. Plasma concentrations increased as dose strength and frequency of dosing were increased.

The ruxolitinib terminal half-life following oral administration is approximately 3 hours with no appreciable accumulation of either parent or metabolites with BID oral dosing. However, the long apparent half-life (~4 days) observed in topical treatment is due to the slow absorption from the skin, which acts as a depot (Study INCB 18424-202). Therefore, the plasma concentration of ruxolitinib (following its topical application) reaches steady-state in 2 to 4 weeks and remains relatively unchanged after steady-state is reached, and this was confirmed in Study INCB 18424-203 and Study INCB 18424-211.

Preliminary PK data are available for adolescents (aged ≥ 12 to 17 years) with AD (Study INCB 18424-102). Plasma concentrations of ruxolitinib were time-dependent with higher concentrations on Day 1 and decreasing concentrations on Day 15 and Day 29. The observed decrease in ruxolitinib blood levels at Week 4 probably relates to a changing proportion of diseased to healthy skin treated at that timepoint and immediately before it. Steady-state plasma concentrations (based on geometric mean) following 1.5% BID in adolescent participants is similar to that in adults, suggesting similar skin flux in the 2 age groups.

Further information on clinical PK is summarized within ruxolitinib cream IB Section 5.2.

2.1.3. Clinical Efficacy and Safety of Ruxolitinib Cream in Vitiligo

The clinical efficacy and safety in vitiligo of ruxolitinib cream was evaluated in Study INCB 18424-211, a Phase 2, randomized, double-blind, vehicle-controlled study conducted in adults with vitiligo who have depigmented areas including at least 0.5% BSA on the face and at least 3% BSA on nonfacial areas. In the first part of the study, a total of 157 participants were equally randomized to receive ruxolitinib cream 1.5% BID, 1.5% QD, 0.5% QD, 0.15% QD, or vehicle BID for 24 weeks. In the second part of the study, all participants initially randomized to vehicle BID and participants initially randomized to 0.15% QD who did not achieve ≥ 25% improvement from baseline in F-VASI were re-randomized to 1 of the 3 higher dosing groups for an additional 28 weeks. All other participants maintained the same treatment until Week 52. After Week 52, participants could receive open-label 1.5% BID for an additional 52 weeks. The primary endpoint was the proportion of participants who achieved a ≥ 50% improvement from baseline in F-VASI50 at Week 24.

All ruxolitinib treatment arms demonstrated clinically meaningful efficacy and superiority over vehicle. The proportion of participants who achieved an F-VASI50 at Week 24 was statistically significantly greater for ruxolitinib cream versus vehicle with response rates of 32.3%, 25.8%, 50.0%, and 45.5% for ruxolitinib cream 0.15% QD, 0.5% QD, 1.5% QD, and 1.5% BID, respectively, and 3.1% for vehicle. The proportion of participants who achieved an F-VASI75 at Week 24 was also statistically significantly greater for ruxolitinib cream versus vehicle with

response rates of 9.7%, 16.1%, 16.7%, and 30.3% for ruxolitinib cream 0.15% QD, 0.5% QD, 1.5% QD, and 1.5% BID, respectively, and 0% for vehicle. For the participants who were initially randomized to ruxolitinib cream 0.5% QD, 1.5% QD, and 1.5% BID and continued on these treatments until Week 52, continued improvement in F-VASI response was observed with the proportion of participants who achieved an F-VASI75 at Week 52, demonstrating response rates of 29.0%, 30.0%, and 51.5% for ruxolitinib cream, respectively.

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

All ruxolitinib treatment arms were generally safe and well-tolerated with no significant TEAEs or application site events and no clinically relevant hematological changes. The TEAE rate overall was low and similar between active treatment and vehicle. There were 4 SAEs through 52 weeks, none of which were treatment-related. Discontinuations from treatment through 52 weeks was low. Safety and tolerability were similar between the Week 24 and Week 52 period.

Efficacy and safety data from the ongoing Phase 3 studies in vitiligo (INCB 18424-306 or INCB 18424-307) are not yet available.

Further information on clinical efficacy and safety in vitiligo patients as well as other indications (psoriasis and AD) is summarized in ruxolitinib cream IB Section 5.3.

2.2. Study Rationale

This study is designed to evaluate the duration of response following withdrawal of ruxolitinib cream (Cohort A vehicle group) and maintenance of response with continued use of ruxolitinib cream in individuals with vitiligo who have experienced repigmentation with ruxolitinib cream treatment. This study is also designed to characterize the long-term efficacy and safety profile of ruxolitinib cream in individuals with vitiligo treated for up to a total of 104 weeks.

2.2.1. Scientific Rationale for Study Design

Findings from the Phase 2 study, INCB 18424-211, suggest that JAK inhibition is an effective therapeutic strategy to treat patients with vitiligo (see Section 2.1.3). The objective of this extension study and its parent studies is to confirm and extend the Phase 2 study efficacy and safety findings for ruxolitinib cream in a larger patient population.

The current Phase 3 extension study is designed to evaluate the long-term efficacy, safety, and tolerability of ruxolitinib cream. Combined with data from its Phase 3 parent studies, this study will provide efficacy and safety data in patients with vitiligo treated for up to 104 weeks with ruxolitinib cream 1.5% BID.

This extension study will enroll interested and eligible participants from the study population of the parent studies. The eligibility criteria used in the parent studies were generally designed to enroll a representative segment of the vitiligo patient population. The parent studies enrolled

both male and female participants (the prevalence of vitiligo is similar between men and women) with non-segmental (generalized) vitiligo, which is the most common type of vitiligo, accounting for up to 90% of cases (Taieb et al 2009). While the Phase 2 study enrolled participants 18 years or older, in the parent Phase 3 studies, participants ≥ 12 years of age were enrolled; this is important because almost 50% of vitiligo patients present before 20 years of age (Rodrigues et al 2017). The emerging safety profile supports enrolling this population of adolescents as ruxolitinib cream has been well-tolerated in the Phase 2 vitiligo study and the AD studies, including Study INCB 18424-102, which enrolled participants with AD aged 12 to 18 years. Additionally, enrollment in the parent studies targeted participants who were amenable to topical therapy of their vitiligo with depigmented areas including ≥ 0.5% BSA on the face, ≥ 0.5 F-VASI, ≥ 3% BSA on nonfacial areas, ≥ 3 T-VASI, and total body vitiligo area ≤ 10% BSA (facial and nonfacial). This extension study will thus be composed of participants meeting these same criteria.

This study includes a 52-week vehicle group; however, participants randomized to vehicle will have already received at least 28 weeks of treatment with ruxolitinib cream 1.5% BID in the parent study, and only participants who have already achieved complete or near-complete response (ie, achieve ≥ F-VASI90) at the time of randomization in this extension study treatment will be subject to randomization to vehicle. Additionally, if participants randomized to vehicle experience relapse (< F-VASI75), they will receive open-label rescue treatment of ruxolitinib cream 1.5% BID until they treatment. Thus, under the design of this study, no participants will go untreated if they experience a clinically meaningful recurrence after withdrawal of active treatment. Including this vehicle group for participants with ≥ F-VASI90 allows for a robust examination of the duration of response following ruxolitinib cream withdrawal.

Inclusion of participants who have achieved ≥ F-VASI90 and are randomized to ruxolitinib cream 1.5% BID allows for an assessment of the maintenance of response with continued use of ruxolitinib cream. Additionally, inclusion of participants who did not achieve ≥ F-VASI90 and are assigned to ruxolitinib cream 1.5% BID allows for an assessment of the maintenance of response and an evaluation of the time course of response with continued use of ruxolitinib cream in individuals who may be exhibiting slower response times. For both of these groups, the additional 52 weeks of treatment in this extension study is designed to further evaluate the long-term efficacy and safety of ruxolitinib cream 1.5% BID treatment.

The primary and key secondary endpoints in this study evaluate the duration of clinical response and the maintenance of response as measured by F-VASI. VASI is recognized as a validated quantitative scale developed by Hamzavi et al (2004). Areas affected by depigmentation due to vitiligo will be assessed using the VASI, which is a quantitative clinical tool that is analogous to the PASI used in psoriasis and is based on a composite estimate of the overall area of vitiligo patches at baseline and the degree of macular repigmentation within these patches over time. In this extension study, both F-VASI and T-VASI will be evaluated. F-VASI was the primary endpoint in the Phase 2 study and was found to accurately reflect the repigmentation response and discern clinically relevant differences in efficacy levels of individual treatment regimens. In addition, from the patient's perspective, facial disease involvement has the strongest relevance on appearance and correlation to the patient's psychological burden. Prior to the earlier parent Phase 3 studies, the sponsor performed additional analyses to evaluate the reliability, validity, ability to detect change, and score interpretability of the VASI instrument based on clinical data from the Phase 2 study. The results indicate that the instrument met or exceeded the standards

for reliability, validity, and ability to detect change. These analyses of treatment efficacy support the clinical relevance of the F-VASI and T-VASI endpoints for vitiligo.

Considering findings from the INFO study (International Initiative for Outcomes [INFO] for Vitiligo; Eleftheriadou et al 2012), INCB 18424-211 results, and the methods used in the parent studies, a number of measures are incorporated into this extension study. In contrast to the Phase 2 study, the primary outcome measure is the F-VASI75 as this represents a higher degree of response for the face. The VNS has been included as a secondary measure. This is a recently validated measure to address the question of satisfactory repigmentation from the patient perspective as the INFO study identified cosmetic acceptability of repigmentation to be of high importance to patients. Other measures included in this study are the [redacted], [redacted], [redacted], DLQI (CDLQI), [redacted]. Relationships between improvement and VASI score improvements in these parameters will be examined.

2.2.2. Justification for Dose

The safety and efficacy outcomes from the Phase 2 study, INCB 18424-211, can be summarized as follows:

- All ruxolitinib cream treatment arms 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 separate 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%). 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 hematological changes through Week 52.

Based on the above data, the proposed treatment regimen of ruxolitinib cream for the Phase 3 studies is 1.5% BID. Limiting treatment to up to 10% BSA will limit exposure and potentially improve the benefit-risk.

2.3. Benefit/Risk Assessment

In nonclinical studies, ruxolitinib cream did not act as a contact sensitizer, nor did it produce significant dermal irritation or demonstrate phototoxicity or photoallergenic 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 treatment for 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 rheumatoid arthritis participants with greater bone marrow reserve, the effects on hematopoietic proliferation appear to be less pronounced. Owing to its low systemic bioavailability, ruxolitinib cream is not expected to bring about clinically significant changes in hematology laboratory investigations.

Based on Week 24 and Week 52 results of the Phase 2 study, INCB 18424-211, all active treatment groups were found to have no clinically relevant AEs related to the treatment regimens and were well-tolerated on application sites. They 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 ruxolitinib cream IB.

3. OBJECTIVES AND ENDPOINTS

Table 4 presents the objectives and endpoints.

Table 4: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the duration of clinical response of ruxolitinib cream in participants with vitiligo.	For participants who are randomized in Cohort A: • Time to relapse (defined as < F-VASI75).
Key Secondary	
To evaluate the duration of clinical response of ruxolitinib cream in participants with vitiligo.	For participants who are randomized in Cohort A: • Time to maintain ≥ F-VASI90 response.
Secondary	
To further evaluate the efficacy of ruxolitinib cream.	• Proportion of participants who achieve F-VASI50/75/90 during the extension treatment period. • Actual measurements, change, and percentage change from baseline in F-VASI. • Proportion of participants who achieve T-VASI50/75/90 during the extension treatment period. • Actual measurements, change, and percentage change from baseline in T-VASI. • Actual measurements, change, and percentage change from baseline in F-BSA. • Actual measurements, change, and percentage change from baseline in T-BSA. • Proportion of participants achieving a VNS of "4 – A lot less noticeable" or "5 – No longer noticeable" during the extension treatment period.
To determine the participants' quality of life	• Change from Week 52 in DLQI (or CDLQI) during the extension treatment period.
To evaluate the safety and tolerability of ruxolitinib cream.	• The frequency and severity of AEs; includes performing physical examinations and collecting vital signs and laboratory data for hematology and serum chemistry.
To evaluate the ruxolitinib PK in plasma after treatment with ruxolitinib cream.	• Trough plasma concentrations of ruxolitinib at Week 80 and Week 104.

Table 4: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3, double-blind, vehicle-controlled, randomized withdrawal and treatment extension study that will enroll eligible participants who have completed either Study INCB 18424-306 or Study INCB 18424-307 (parent studies) in which the participants will have been using ruxolitinib cream 1.5% BID for the previous 28 to 52 weeks (depending on their initial randomization in the parent study; see Figure 1).

The parent studies are randomized, vehicle-controlled studies in adolescent and adult participants (age ≥ 12 years) with non-segmental vitiligo who have depigmented area 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) was not to exceed 10% BSA. Approximately 300 participants per each parent study were to be randomized 2:1 to receive an initial, double-blind study treatment of ruxolitinib cream 1.5% BID or vehicle (applied to depigmented vitiligo areas on the face and body up to 10% total BSA) for 24 weeks. After completion of the Week 24 assessments, participants in these studies were offered the opportunity to receive an additional 28 weeks of open-label treatment extension with ruxolitinib cream 1.5% BID under the parent study protocol.

Participants who successfully complete the 52-week treatment in either of the parent studies (ie, 52 weeks ruxolitinib cream or 24 weeks vehicle plus 28 weeks ruxolitinib cream) and tolerated ruxolitinib treatment without safety concern and with good compliance for continuation may be eligible to participate in this treatment extension study.

Visits in this treatment extension study are named to reflect continuation from the parent studies, with the first visit of this treatment extension study occurring at Week 52. The eligibility assessment for this extension study occurs at Week 52. The treatment extension period of this study comprises the period from the Week 52 visit to the Week 104 visit (inclusive). Following the last application of study treatment at Week 104, there will be a 30-day safety follow-up period to evaluate safety and duration of response. Figure 1 presents the study design schema, and Table 3 presents the SoA.

The purpose of this extension study is to evaluate the duration of response under randomized withdrawal of ruxolitinib cream and maintenance of response with continued use of ruxolitinib cream, in vitiligo patients who have experienced repigmentation with ruxolitinib cream treatment, as well as to provide long-term efficacy and safety data in vitiligo patients, regardless of how quickly or completely they responded to treatment initially. Eligible participants in this study will be assigned to 1 of 2 cohorts, Cohort A or Cohort B, based on their F-VASI responses at the time of enrollment in this study (ie, at Week 52).

Treatment in Cohort A is a randomized withdrawal design and will provide data on the duration of response following withdrawal of ruxolitinib cream and maintenance of response with its continued use. Participants who achieve complete or almost complete facial repigmentation (ie, achieve ≥ F-VASI90) at Week 52 in the parent study will be assigned to Cohort A and will be stratified by the original treatment received on study Day 1 of the parent study and randomized 1:1 to treatment with vehicle cream BID or ruxolitinib cream 1.5% BID for an additional 52 weeks (ie, until EOT at Week 104). However, any participants in Cohort A who

experience relapse (defined as < F-VASI75) will receive ruxolitinib cream 1.5% BID as an open-label rescue treatment until they complete treatment (Week 104 or EOT).

Treatment in Cohort B will provide long-term efficacy and safety data for ruxolitinib cream in vitiligo patients. Participants who did not achieve ≥ F-VASI90 at Week 52 of the parent studies will be assigned to Cohort B and will continue ruxolitinib cream 1.5% BID for 52 weeks (ie, until EOT Week 104).

For Cohort A, the participant, investigator, and sponsor will remain blinded to treatment assignment; the treatment for Cohort B will be open-label.

During this extension study, participants will receive study treatment (ruxolitinib cream 1.5% BID or vehicle) for 52 weeks to be applied to depigmented areas on the face and body; the total treated areas (facial plus nonfacial areas) should not exceed 10% BSA. Participants should continue to treat depigmented areas identified for treatment at baseline of the parent study even if the area begins to improve or fully repigment.

Thus, depending on their initial randomized treatment in the parent study and the treatment to which they are randomized at Week 52 in this extension study, participants will have received ruxolitinib cream 1.5% BID for a minimum of 28 weeks and a maximum of 104 weeks.

Safety endpoints, such as nature of AEs (type, frequency, and severity includes performing targeted physical examination and collecting vital signs and routine laboratory investigations) will be monitored and recorded throughout the course of this study.

4.2. Overall Study Duration

Eligibility will be evaluated on the first day of this extension study, which occurs on the same day as the parent study Week 52 visit; the treatment extension period is 52 weeks; and safety follow-up is 30 days. Total duration of this study is approximately 56 weeks (see Figure 1).

The study will begin when the first participant (or parent or guardian) signs the 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.

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 in writing of the study's completion or early termination, 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. Currently enrolled and receiving treatment in INCB 18424-306 or INCB 18424-307 studies evaluating ruxolitinib cream in participants with vitiligo.

   Note: Eligibility criteria for INCB 18424-306 or INCB 18424-307 are provided in Appendix A.

2. Currently tolerating ruxolitinib cream in the parent study and no safety concerns per investigators judgment.
3. Has demonstrated compliance, as assessed by the investigator, with the parent study protocol requirements.
4. Willingness and ability to comply with scheduled visits, treatment plans, and any other study procedures indicated in this protocol.
5. Male and female participants must be willing 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. Females of non-childbearing potential (ie, or surgically sterile with a hysterectomy and/or bilateral oophorectomy OR postmenopausal, ≥ 12 months of amenorrhea without an alternative medical cause).
   b. Prepubescent adolescents (age 12-18 years old at the time enrolled in parent studies).
   Note: Information about specific types of acceptable contraceptive measures and duration of contraceptive use are provided in Appendix B.
6. For adult participant, ability to comprehend and willingness to sign an ICF; for adolescent participant, written informed consent of the parent(s) or legal guardian and written assent from the adolescent participant when possible.

   Note: Adolescents, who during the course of the study become legal adults, will be asked for their consent to continue the study, and in the event of lack thereof, will be discontinued from further participation.

5.2. Exclusion Criteria

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

1. Has been permanently discontinued from study treatment in the parent study for any reason.
2. Participants with an uncontrolled intercurrent illness or any concurrent condition that, in the investigator's opinion, would jeopardize the safety of the participant or compliance with the Protocol.

   Note: See information provided in Exclusion Criterion 4 of the INCB 18424-306/ INCB 18424-307 parent study protocol (Appendix A); the investigator should consult with the sponsor medical monitor if there are any questions regarding uncontrolled intercurrent illness or any concurrent condition that may be exclusionary.
3. Pregnant or breastfeeding woman.
4. Participants who live with anyone participating in any current Incyte-sponsored ruxolitinib cream study.

5.3. Lifestyle Considerations

Participants should continue to avoid excessive exposure to artificial sunlight (including tanning booths, 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.

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

5.4. Screen Failures

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

5.5. Replacement of Participants

Participants will not be replaced during the study.

6. STUDY TREATMENT

See Appendix D for COVID-19–related guidance.

6.1. Study Treatments Administered

Table 5 presents the study treatment information.

Table 5: Study Treatment Information

Study treatment name:	Ruxolitinib	Vehicle
Dosage formulation:	Cream	
Unit dose strength(s)/dosage level(s):	1.5%	Not applicable
Route of administration:	Topical	
Administration instructions:	BID. A thin film is applied to depigmented vitiligo areas.	BID. A thin film is applied to the depigmented vitiligo areas.
Packaging and labeling:	Ruxolitinib cream and vehicle cream will be provided in 60 g tube. 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

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

At any time, if vitiligo areas become significantly more extensive than from the previous visit, the participant should contact the study site to discuss with the investigator whether additional evaluation at the clinic is required. If any other skin products that are permitted under the study Protocol are used, participants should continue these unchanged during the study.

During the treatment extension period, participants should follow the below study drug application guidance:

- All participants in Cohort A will use their randomly assigned treatment (either vehicle or ruxolitinib cream) on both the face and total body.
- Participants should apply study drug to depigmented vitiligo areas up to a T-BSA (facial and nonfacial) of ≤ 10% BSA.

- Participants should continue to treat all depigmented vitiligo areas identified for treatment at baseline (Day 1 of the parent study) even if the area begins to improve or fully repigment.
- Participants who have an expansion of existing areas of vitiligo or develop new vitiligo lesions during the course of the treatment extension period may treat these areas after a visit to document the VASI score and other measures of vitiligo (may be unscheduled visit), as long as the new treated T-BSA (facial and nonfacial) does not exceed 10% BSA. Newly developing vitiligo lesions should be documented in the eCRF. The VASI scores for these new lesions should not be calculated with or combined together with treated areas identified at baseline (Day1 of parent study).

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 treatments received and that any discrepancies are reported and resolved before use of the study treatment.

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

All study treatment 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 treatment 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 drug(s) to the study site.
- Inventory of study drug(s) at the site.
- Participant use of the study drug(s) including tube counts from each supply dispensed.
- Return of study drug(s) 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 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 treatments are provided 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. For Cohort A, the system will assign in a 1:1 ratio (ruxolitinib cream 1.5% BID:vehicle). For Cohort B, the system will assign all participants to ruxolitinib cream 1.5% BID.

The IRT will track participant visits, randomize participants according to the defined parameters, maintain the blinding (Cohort A only), 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).

For Cohort A, the participant, investigator, and sponsor will remain blinded to treatment assignment; the treatment for Cohort B will be open-label. After the database lock for the primary analysis (Week 104), the participant, the investigator, and the sponsor 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 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 within 70% to 130% of the prescribed number of applications. Participants will be instructed to bring all study drugs 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 Application Interruptions and Modifications of Study Drug

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

In some circumstances, it may be necessary to temporarily interrupt treatment with study drug (ruxolitinib cream or vehicle cream). Except in cases of emergency, it is recommended that any findings of concern (eg, AE) be confirmed and that the investigator consult with the sponsor medical monitor (or other representative of the sponsor) before interrupting study 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 and the AE is confirmed related to the study drug may need the study drug to be permanently discontinued.

Instructions for application interruptions of study treatment are outlined in Table 6. 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 drug and the participant's underlying condition.

Table 6: 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 lab 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 treatment 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 reviewed at each study visit. Any concomitant medication/treatment received from the first dose of study treatment in this extension study through 30 days after the last dose of study treatment will be recorded in the eCRF. Any addition, deletion, or change in the dose of these medications will also be recorded. 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 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 judgement with these recommendations and adhere to the guidelines as closely as possible. The sponsor should be consulted if there are specific questions.

- Participants may use bland emollients or camouflage makeup.

  Note: Emollients or camouflage makeup should not be used within 2 hours after study drug application. The study drug may not be applied over sunscreen 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) from the time of the Week 52 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) from the time of the Week 52 visit through the safety follow-up visit, unless deemed acceptable by the investigator.
- Participants should not take baths or showers within 2 hours after study drug application.
- Treatment for dermatologic disease besides vitiligo (eg, AD or psoriasis) is allowed for areas not being treated for vitiligo:
  - It involves < 10% of the BSA outside of the areas treated for vitiligo.
  - Topical tacrolimus, pimecrolimus, or corticosteroids Class 6 or 7 (or low potency per WHO classification; see Appendix C) are at a stable dose.
  - Topical corticosteroids Class 1 through 5 (see Appendix C) are used for no longer than 7 sequential days and no more than 14 days in total.
- Use of oral corticosteroids for no longer than 7 days if deemed acceptable by the investigator and the sponsor for nondermatologic conditions (eg, asthma exacerbation, bronchitis).

6.6.3. 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 drugs.
- Treatment known to affect the course of vitiligo, such as skin bleaching treatments (eg, hydroquinone) or depigmenting agents (eg, monobenzone)

  Note: Skin bleaching (eg, hydroquinone) use is prohibited during the study but is allowed as prior therapy.
- Other topical agents (except those in Section 6.6.1) or treatments for vitiligo (including corticosteroids [topical, systemic, or oral], vitamin D derivatives, calcineurin inhibitors, laser or surgical treatments, phototherapy, or other procedures).
- Biological therapies or other immunosuppressant agents.
- Any phototherapy, including tanning beds.
- Live or live-attenuated vaccination.

6.7. Rescue Treatment

For participants in Cohort A, if there is a loss of clinically meaningful response on the face (ie, < F-VASI75) at any time, the participants will receive open-label ruxolitinib cream 1.5% BID until completing the study (ie, Week 104 or EOT).

6.8. Treatment After the End of the Study

No treatment will be provided to participants after the end of the study.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

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

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

  Note: Consent withdrawn means that the participant has explicitly indicated that they do not want to be followed any longer; in this case no further data, except data in public domain, may be solicited from or collected 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 one 60 g tube per week.
- 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, the EOT visit should be conducted. Reasonable efforts should be made to have the participant return for a safety follow-up visit. These visits are described in Table 3. The last date of the last dose of study treatment and the reason for discontinuation of study treatment will be recorded in the eCRF.

If a participant is discontinued from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal must be documented in the participant's medical record and the primary reason for withdrawal must be included in the eCRF.
- The EOT visit should be performed.
- The date of the EOT visit should be recorded in the eCRF.
- Participants must be followed for safety until the time of the safety follow-up visit or until study 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/efficacy 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 the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

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

See Table 3 for data to be collected at the time of study discontinuation and safety 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/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. The participant will be counseled regarding the importance of maintaining the assigned visit schedule, and the site 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 D 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/assent must be obtained before any study-related procedures are conducted, unless otherwise specified by the protocol.

    Note: Adolescent participants who become legal adults during the study will be asked for their signed consent to continue the study, and in the event of lack thereof, will be discontinued from further participation.
  - Informed consent/assent 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/assent template. The ICF/assent must include a statement that the sponsor or its designee and regulatory authorities have direct access to participant records.
  - The ICF/assent 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(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

8.1.2. Eligibility Procedures

All information associated with eligibility requirements must be entered into the appropriate eCRF pages.

Results from the eligibility assessments will be reviewed by the investigators to confirm eligibility before administration of study treatment in this extension study.

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; this will be the same participant ID number as assigned in the parent study. Upon determining that the participant is eligible for study entry, the IRT system will be contacted to obtain the study medication 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 Week 52 visit and each visit thereafter, 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 Week 52 and at all visits (through Week 92). The reminder card will indicate the date/time of the next visit and will also remind the participant that they should have their application at the clinic during the visit under site supervision after their blood draws for PK and safety evaluations have been completed.

8.2. Efficacy Assessments

8.2.1. Body Surface Area

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

8.2.2. Vitiligo Area Scoring Index

Areas affected by depigmentation due to vitiligo will be assessed using the VASI. It is based on a composite estimate of the overall area of vitiligo patches at baseline and the degree of macular repigmentation within these patches over time.

Facial VASI is measured by percentage of vitiligo involvement (% of BSA) and the degree of depigmentation. The percentage of BSA (hand unit) vitiligo involvement is estimated by the investigator using the Palmar Method (see Section 8.2.1). Hand unit is based on participant's hand size. Investigator uses his/her hand to mimic the participant's hand size to evaluate percentage of BSA vitiligo involvement. The degree of depigmentation for each vitiligo involvement site is determined and estimated to the nearest of the following percentages: 0, 10%, 25%, 50%, 75%, 90%, or 100%. At 100% depigmentation, no pigment is present; at 90%, specks of pigment are present; at 75%, the depigmented area exceeds the pigmented area; at 50%, the depigmented and pigmented area are equal; at 25%, the pigmented area exceeds the depigmented area; at 10%, only specks of depigmentation are present. The F-VASI is then derived by multiplying the values assessed for the vitiligo involvement by the percentage of affected skin for each site on the face and summing the values of all sites together (possible range 0-3).

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

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

$$VASI = \Sigma\ [hand\ units] \times [Residual\ Depigmentation]\ all\ body\ sites$$

The body is divided into the following 6 separate and mutually exclusive sites: (1) head/neck, (2) hands, (3) upper extremities (excluding hands), (4) trunk, (5) lower extremities (excluding feet), and (6) feet. The percentage of vitiligo involvement is estimated in hand units (% of BSA) by the same investigator during the entire course of the study. Hand unit is based on participant's hand size. The investigator uses his/her hand to mimic the participant's hand size to

evaluate % BSA vitiligo involvement. The degree of depigmentation for each body site is determined and estimated to the nearest of the following percentages: 0, 10%, 25%, 50%, 75%, 90%, or 100%. The T-VASI is then derived by multiplying the values assessed for the vitiligo involvement by the percentage of affected skin for each body site and summing the values of all body sites together (Hamzavi et al 2004).

Full details will be provided in the Study Manual.

[redacted]

[redacted]

8.2.5. Photography

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

All sites will use 2D photography, and selected sites will also use 3D photography, to photograph areas of the participant's face affected with vitiligo. 2D photography will be used at all sites for the target nonfacial depigmented area.

Target nonfacial vitiligo depigmented area definition: At the baseline visit (Day 1) of the parent study (INCB 18424-306 or INCB 18424-307), depigmented nonfacial areas that are representative of the participant's overall disease and that are to be treated with study drug will have been selected as targeted nonfacial vitiligo depigmented areas. These same areas will be assessed, measured, and documented in the participant's medical record at each visit of this treatment extension study (see Table 3). The genitalia area should not be photographed.

Ad hoc photography of skin-related AEs is recommended.

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

8.2.6. Patient-Reported Outcomes

Quality of life will be assessed (see Table 3) using the following tools:

- VNS (Section 8.2.6.1);
- [redacted]
- DLQI/CDLQI (Section 8.2.6.5);
- [redacted]

In order to avoid bias in the participants' responses to the questionnaires, all these assessments should be completed before any other evaluations or study procedures on the day of the study visit and before discussions with the investigator or study site staff.

8.2.6.1. Vitiligo Noticeability Scale

The VNS is a patient-reported measure of vitiligo treatment success, which has a 5-point scale (Batchelor et al 2016). The baseline facial photograph from the parent study (INCB 18424-306 or INCB 18424-307) will be shown to the participants for reference and a mirror will be provided for the participants to assess the vitiligo on their face. The participant will be asked to respond to the following query:

> Compared with before treatment, how noticeable is the vitiligo now? Responses: (1) More noticeable, (2) As noticeable, (3) Slightly less noticeable, (4) A lot less noticeable, and (5) No longer noticeable.

VNS scores of 4 or 5 can be interpreted as representing treatment success.

[redacted]

[redacted]

8.2.6.5. Dermatology Life Quality Index

The DLQI is a simple, 10-question validated questionnaire to measure how much the skin problem has affected the participant over the previous 7 days (Finlay and Khan 1994). Participants age ≥ 16 years will answer the questionnaire with (1) very much, (2) a lot, (3) a little, or (4) not at all.

The questionnaire is analyzed under 6 headings as follows:

- Symptoms and feelings (Questions 1 and 2);
- Daily activities (Questions 3 and 4);
- Leisure (Questions 5 and 6);
- Work and school (Question 7);

- Personal relations (Questions 8 and 9);
- Treatment (Question 10).

CDLQI is the youth/children's version of the DLQI. For participants who are age < 16 years at baseline (Day 1) of the parent study (INCB 18424-306 or INCB 18424-307), the CDLQI will be completed instead of the DLQI throughout their participation in this extension study. This questionnaire is self-explanatory and can be simply given to the participant who is asked to fill it in and who may ask the help of the parent or guardian. The questionnaire is analyzed under 6 headings as follows:

- Symptoms and feelings (Questions 1 and 2);
- Leisure (Questions 4, 5, and 6);
- School or holidays (Question 7);
- Personal relationships (Questions 3 and 8);
- Sleep (Question 9);
- Treatment (Question 10).

Full details will be provided in the Study Manual.

Full details will be provided in the Study Manual.

8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Table 3).

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 treatment. Adverse events 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. 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 treatment, or that caused the participant to discontinue the study treatment. 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 between visits or through physical examinations, laboratory tests, or other assessments. The definition, reporting, and recording requirements for AEs are described in Section 9.

The investigator will submit any updated SAE data to the sponsor 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).

8.3.2. Physical Examinations

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

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 neurological examination will also be performed.

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

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

8.3.3. Vital Signs

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, semi-recumbent, 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. Laboratory Assessments

Required laboratory tests are listed in Table 9, which include serum chemistry, hematology, and pregnancy testing (see Table 3 for timing of laboratory assessments). Clinical laboratory tests will be performed at a central laboratory (refer to the Laboratory Manual for sample handling and shipping instructions).

Clinically significant abnormal laboratory findings are those that 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 treatment, 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 9: Required Laboratory Analytes

Serum Chemistries[a]	Hematology	Pregnancy Testing
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	Complete blood count, including: • Hemoglobin • Hematocrit • MCV • Platelet count • Mean platelet volume • Red blood cell count • Reticulocyte count • White blood cell count Differential count, including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils	Female participants of childbearing potential have a serum test at Week 52 and at the safety follow-up visit. A urine test will be conducted at all other visits. A positive urine test will be confirmed by a serum test.

Note: Additional tests may be required, as agreed upon by the investigator and sponsor, based on emerging safety data.
[a] All serum chemistries will be performed on samples collected without respect to food intake (ie, nonfasting).

8.3.4.1. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential during the Week 52 visit and at the safety follow-up visit (30 [+ 7] days after EOT). Urine pregnancy tests will be conducted as outlined in Table 3, as medically indicated, or per country-specific requirement. Urine pregnancy tests will be performed locally. If a urine pregnancy test is positive, the results 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 9.6 for reporting requirements.

8.4. Pharmacokinetic Assessments

Venous blood samples will be collected to assess the PK of ruxolitinib cream in participants at each study visit indicated in Table 3.

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

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

Pharmacokinetic blood samples can be collected at any time prior to study drug application at the site at the Week 80 visit and at any time at the W104 (EOT) visit. Blood samples must not be drawn from the area that has been treated with study drug. If it is not possible to access an area that is not treated with study drug, the site must adequately document this in the eCRF and not take the PK blood sample for that visit. After the PK sample is drawn, participants will apply ruxolitinib cream 1.5% or vehicle cream at the site.

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

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

8.8. Safety Follow-Up

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

Adverse events and SAEs must be reported up until at least 30 days after the last dose of study drug, the date of the safety follow-up visit, or 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 considered drug-related. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.
Events <u>Meeting</u> 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). • Abnormal laboratory test results constitute 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 lab result (eg, low hemoglobin, platelet count decreased). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the Adverse Event Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition or considered to be treatment-related by the investigator. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE if it occurred after signing the ICF. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

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 occurred. 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 (usually 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 of a pre-existing condition that did not worsen from baseline is not considered an AE.
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. Other situations (Important Medical Event)

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 invasive or malignant cancers (excluding the disease[s] under study in oncology protocols), intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics 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 AE eCRF page.
- There may be 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 on the copies of the medical records before submission.
- 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 severity grade (CTCAE 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 final safety follow-up.
- 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 Adverse Event Form, and the treatment should be specified on the appropriate eCRF (eg, 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 treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are 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 relationship.
- The investigator will also consult the RSI in the ruxolitinib cream IB in his/her assessment.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment 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 to the sponsor or designee. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data** to the sponsor or designee**.**
  - The investigator may change his/her opinion of causality in light of follow-up information and send a follow-up SAE report with 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 or designee to elucidate the nature and/or causality of the AE/SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.
- If a participant dies during participation in the study or during a recognized safety follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings, including histopathology.
- New or updated information will be recorded in the originally completed eCRF.

- Any updated SAE data will be submitted to the sponsor or designee immediately, without undue delay, under no circumstances later than 24 hours following knowledge of the event.
- Once an AE is detected, it should be followed 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 until the event resolves.

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 treatment, 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 treatment 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 towards the safety of participants and the safety of a study treatment under clinical investigation are met.

If the SAE is not documented in the ruxolitinib cream IB for the study drug (new occurrence) and is thought to be related to the sponsor's 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 treatment 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 SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a 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. Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form. • Facsimile or email transmission of the Serious Adverse Event Report Form is the preferred method to transmit this information to the PhV/designee. The contact information of the sponsor's study-specific representatives is listed in the Study Manual provided to each site. The original copy of the Serious Adverse Event Report Form and the confirmation sheet must be kept at the study site. • Follow-up information is recorded 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. • In rare circumstances and in the absence of facsimile or computer equipment, notification by telephone is acceptable with a copy of the Incyte Serious Adverse Event Report Form sent by overnight mail or courier service. Initial notification via telephone does not replace the need for the investigator to complete and sign the Serious Adverse Event Report Form within the designated reporting time frames. • Contacts for SAE reporting can be found in the Study Manual.

9.5. Emergency Unblinding of Treatment Assignment

In a medical emergency, 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 be withdrawn from the study treatment, unless there are ethical reasons to have the participant remain on the study treatment. 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.

9.6. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that 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.
- 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 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.

9.7. 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 ruxolitinib cream 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.

9.8. 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.

9.9. 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

Any eligible participants will be enrolled from the 2 parent Phase 3 studies, INCB 18424-306 and INCB 18424-307. The sample size is not based on any statistical power calculations.

10.2. Populations for Analysis

Table 10 presents the populations for analysis.

Table 10: Populations for Analysis

Population	Description
Full analysis set (FAS)	All participants enrolled in the study who receive at least 1 dose of study drug (ruxolitinib cream or vehicle) at or after Week 52.[a]
Intent-to-treat in long-term extension (ITT-Ext)	All participants who achieve ≥ F-VASI90 at Week 52[a] and are randomized. Treatment groups for this population will be defined according to the treatment assignment at the time of randomization regardless of the actual study medication the participant might take the study.
PK evaluable	The PK evaluable population includes participants who received at least 1 dose of ruxolitinib cream and provided at least 1 measurable postdose PK sample/assessment. The study pharmacokineticist will review data listings of participant administration and sample records to identify participants to be excluded from the analysis.
PK/PD evaluable	The PK/PD evaluable population includes participants who received at least 1 dose of study drug (ruxolitinib cream or vehicle) and provided at least 1 measurable/evaluable postdose PK/PD sample/assessment. The study pharmacokineticist will review data listings of participant administration and sample records to identify participants to be excluded from the analysis.

[a] Week 52 is the first visit of the treatment extension study (visits are named to reflect continuation from the parent study).

10.3. Level of Significance

The primary and key secondary endpoints will be tested in a fixed sequence at 2-sided $\alpha = 0.05$ level, that is, the key secondary endpoint will be tested only if the primary is rejected. No formal statistical tests will be performed for other endpoints. All confidence intervals will be 95%.

10.4. Statistical Analyses

10.4.1. Efficacy Analysis

Efficacy endpoints are listed in Section 3.

For all complete or near-complete responders in the ITT-Ext population (defined as achieving F-VASI90 at Week 52) in the treatment extension period, the events can be defined as follows:

- Relapse is defined as a loss of F-VASI75 response assessed as percentage change from the baseline (Day 1 of the parent study) on F-VASI < 75%.
- Loss of complete or near-complete response is defined as participants who do not maintain an F-VASI90.

For relapse, a binary variable event is defined to be equal to 1 (Yes) when the value is greater or equal to 75% and 0 (No) for less than 50%.

For loss of F-VASI90 response, a categorical variable event is defined to be equal to 1 (Yes) when the value is greater or equal to 90% and 0 (No) for less than 90%.

The time to relapse or loss of adequate response is defined as the number of days from the Week 52 randomization to the first evaluation date at which the participant has met the criteria. For participants who discontinue early or who complete without meeting criteria for the event, the time-to-event will be censored and defined as the number of days from the Week 52 randomization to the participant's last evaluation date.

The time to event data will be assessed using the Kaplan-Meier product limit method. Treatment comparisons between ruxolitinib cream 1.5% BID to vehicle will be performed using the log-rank test. Hazard ratios and the corresponding 95% confidence intervals will be estimated using the Cox proportional hazards model.

The incidence of relapse or loss of adequate response following the Week 52 randomization will be summarized by ruxolitinib cream 1.5% BID and vehicle at each timepoint.

Other efficacy endpoints will be summarized in FAS. Descriptive summaries for continuous variables will include, but not be limited to, the number of observations, mean, standard deviation, median, minimum, and maximum. Descriptive summaries for categorical variables will include the number and percentage of participants in each category.

For all relapse participants, the time to regaining F-VASI75/90 response is defined as the number of days from the start of the retreatment of ruxolitinib cream 1.5% BID to the first visit at which the participant has regained the F-VASI75/90 response. For participants who discontinue or complete treatment before regaining F-VASI75/90, the time to regaining F-VASI75/90 is censored. The time to event data will be assessed using the Kaplan-Meier product limit method.

10.4.2. Safety Analyses

Safety endpoints are listed in Section 3. Safety analyses will be conducted using the FAS.

10.4.2.1. 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.

10.4.2.2. 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.

10.4.2.3. Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, pulse, respiratory rate, and body temperature) at each assessment time.

10.4.3. Other Analyses

Pharmacokinetic endpoints are listed in Section 3. The ruxolitinib plasma concentration data collected at study visits will be analyzed using summary statistics. Pharmacokinetic steady state is achieved before Week 4 in vitiligo patients, and therefore all observed ruxolitinib plasma concentrations will be averaged to obtain an overall mean exposure for each participant.

[redacted]

10.5. Interim Analysis

No formal interim analysis is planned in this study.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

- The Protocol, Protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC 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 IRB/IEC approval 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, or 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.
- 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 at the investigator's site.

  - 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. Also, current applicable medical records must be available.

- May have responsibility for 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 privacy laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that sensitive information is handled in accordance with local requirements (eg, HIPAA). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

Participant names will not be supplied to the sponsor or its designee. Only the participant number and the participant's initials (participant's initials will only be recorded if allowable by local regulations) will be recorded in the eCRF, where permitted; 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 local data protection laws.

11.4. Financial Disclosure

Before study initiation, all clinical investigators participating in clinical studies subject to 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 or 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. The sponsor commits to also adhere to supranational/international rules regarding publishing research results, as set by the Helsinki Declaration. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. The terms regarding the publication of study results are contained in the agreement signed with the sponsor or its designee. A signed agreement will be retained by the sponsor or its designee.

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

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

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

11.6. Study and Site Closure

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

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

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

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

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APPENDIX A. ELIGIBILITY CRITERIA FROM STUDIES INCB 18424-306 AND INCB 18424-307

INCB 18424-306 and -307 Inclusion Criteria:

Participants were eligible to be included in study INCB 18424-306 or study INCB 18424-307 only if all of the following criteria applied:

1. Adolescents and adults aged ≥ 12 years.
2. Participants with a clinical diagnosis of non-segmental vitiligo with depigmented area including ≥ 0.5% BSA on the face, ≥ 0.5 F-VASI, ≥ 3% BSA on nonfacial areas, ≥ 3 T-VASI, and total body vitiligo area (facial and nonfacial) not exceeding 10% BSA.
3. Participants who 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.
4. Male and female participants must be willing 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. Females of non-childbearing potential (ie, or surgically sterile with a hysterectomy and/or bilateral oophorectomy OR postmenopausal, ≥ 12 months of amenorrhea without an alternative medical cause).
   b. Prepubescent adolescents.
   Note: Information about specific types of acceptable contraceptive measures and duration of contraceptive use are provided in Appendix B.
5. For adult participant, ability to comprehend and willingness to sign an ICF; for adolescent participant, written informed consent of the parent(s) or legal guardian and written assent from the adolescent participant.

   Note: Adolescents, who during the course of the study become legal adults, will be asked for their consent to continue the study, and in the event of lack thereof, will be discontinued from further participation.

INCB 18424-306 and -307 Exclusion Criteria:

Participants were excluded from study INCB 18424-306 and study INCB 18424-307 if any of the following criteria applied:

1. Participants who have 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. Participants who have used depigmentation treatments (eg, monobenzone) for past treatment of vitiligo or other pigmented areas.

   Note: Prior use of hydroquinone is not prohibited (as it is a bleaching agent, not a depigmentation treatment).

4. Participants with 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, chicken pox) within 1 week before baseline.
    c. Conditions at baseline that would interfere with evaluation of vitiligo.
    d. Any serious illness or medical, physical, or psychiatric condition(s) that, in the investigator's opinion, would interfere with full participation in the study, including 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.
        – Participants with 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 alcoholism 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.
        – Participants who are committed to an institution by virtue of an order issued either by the judicial or the administrative authorities.
5. Participants using 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, metoxypsoralens.

- 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 bed 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. Participants who have previously received JAK inhibitors, systemic or topical.
7. Participants with clinically significant abnormal laboratory values at screening:
   a. Hemoglobin (< 10 g/dL).
   b. Liver function tests:
      - AST or ALT ≥ 2 × ULN.
      - Alkaline phosphatase and/or bilirubin > 1.5 × ULN (isolated bilirubin > 1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%).
   c. Severe renal disease (with creatinine clearance < 30 ml/min) or renal disease requiring dialysis.
   d. Clinically significant abnormal TSH or free T4 at screening as determined by the investigator.
   e. Positive serology test results at screening for HIV antibody.
8. Body mass index < 17 or > 40 kg/m^2 for adult participants (age ≥ 18 years). BMI-for-age in the < 5th percentile or ≥ 85th percentile range for adolescent participants (age ≥ 12 to < 18 years) according to the CDC BMI Percentile Calculator for Child and Teen (2019).

   Note: Adolescent BMI criterion added based on INCB 18424-306 and INCB 18424-307 Protocol Amendment 3-US-CA (dated 13 MAR 2020).
9. Pregnant or lactating participants, or those considering pregnancy during the period of their study participation.
10. Participants who, 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. Participants with known allergy or reaction to any component of the study formulation.
13. Participants who live with anyone participating in any current Incyte-sponsored ruxolitinib cream study.

APPENDIX B. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

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 child-bearing 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. Males 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 less than 1% per year when used consistently and correctly are considered as highly effective birth control methods:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
  - 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[a,b]
- 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 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 less than 1% failure rate methods.

[e] A combination 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 Trial Facilitation and Coordination Group 2014.

APPENDIX C. WHO CLASSIFICATION OF TOPICAL CORTICOSTEROIDS

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

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

Source: WHO 1997.

APPENDIX D. COVID-19 PANDEMIC MITIGATION STRATEGIES AND INSTRUCTIONS

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

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

Study Site Visits

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

- In order to minimize participant risk, study visits (except Week 52 and Week 104 visits) may be conducted via telemedicine modalities (phone or video). At a minimum, a review of AEs, concomitant medications, and study drug compliance must be completed. Periodic on-site visits should be conducted whenever feasible. The physician efficacy assessments must not be conducted by phone or video.
- Week 52 and Week 104 Visits must be conducted in person in their entirety because VASI assessments must be completed by the qualified raters face to face. These visits cannot be missed or conducted remotely. The investigator should document the visit window deviation in the eCRF if necessary.

Investigational Medicinal Product Dispensation and Distribution

In order to ensure the continuity of providing their participants' clinical supplies within the constraints imparted by the pandemic, the site staff can decide to supply study drug to participants. Adequate supplies of study drug as determined by the investigator to cover 12 weeks can be shipped to the participants by the investigator or appropriately delegated staff (eg, the study pharmacy staff) using a third-party service if duly authorized by the participant. The study site may use their own preferred courier, provided the courier adheres to certain standards (eg, use of personal protection equipment, maintenance of temperature-controlled transit environment) or one centrally contracted by the sponsor.

Clinical Trial Monitoring

Study monitoring visits may be postponed; however, the site monitor will continue to employ off-site monitoring practices such as routine communication methods (eg, phone calls, emails, video visits) with the sites to get information on trial progress, participant status, and information on issue resolution. The study monitor may remotely review data entered into the EDC for accuracy and completeness. Remote source data verification may be implemented with agreement of the principal investigator and institution, as applicable.

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

APPENDIX E. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1:	28 SEP 2020
Amendment 2:	10 NOV 2020

Amendment 2 (10 NOV 2020)

Overall Rationale for the Amendment:

The main purpose of this amendment is to add language to the Protocol to inform sites of alternative strategies to guarantee continuity of the clinical trial conduct and oversight in response to the COVID-19 pandemic.

1. **Appendix D, COVID-19 Pandemic Mitigation Strategies and Instructions**

   Description of change: Added Appendix D to the Protocol and added cross-references to the appendix to relevant sections.

   Rationale for change: To provide sites with Protocol-related guidance in response to the COVID-19 pandemic.

2. **Incorporation of administrative changes.** Other minor, administrative changes and clarifications have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 1 (28 SEP 2020)

Overall Rationale for the Amendment: The primary purpose of this amendment is to accommodate the EMA PDCO recommendation regarding the DLQI/CDLQI endpoint and to align the PK endpoints with those of parent studies INCB 18424-306 and INCB 18424 307.

1. **Title Page; Section 1, Protocol Summary**

   Description of change: Added TRuE-V LTE to the Protocol title.

   Rationale for change: To include the short name in the title.

2. **Section 1, Protocol Summary (Table 1: Primary and secondary Objectives and Endpoints); Section 3, Objectives and Endpoints (Table 8: Objectives and Endpoints)**

   Description of change: Moved endpoint for DLQI/CDLQI from exploratory to secondary.

   Rationale for changes: To address EMA PDCO recommendation.

2. **Section 1, Protocol Summary (Table 1: Primary and Secondary Objectives and Endpoints); Section 3, Objectives and Endpoints (Table 8: Objectives and Endpoints)**

   Description of change: Moved endpoint for PK from exploratory to secondary.

   Rationale for change: To align with INCB 18424-306 and INCB 18424-307 parent studies.

3. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 8.4, Pharmacokinetic Assessments**

   Description of change: Added clarifications that PK samples should be collected at predose and the time of the last study drug application is to be recorded in the eCRF.

   Rationale for change: To align PK sample collection procedures with INCB 18424-306 and INCB 18424-307 parent studies.

4. **Section 5.1, Inclusion Criteria (Inclusion Criteria 5a and 6)**

   Description of change: Clarified wording of inclusion criteria.

   Rationale for change: To align with INCB 18424-306 and INCB 18424-307 parent studies.

5. **Section 10.4.3, Other Analyses**

   Description of change: Corrected PK data analysis method.

   Rationale for change: Ruxolitinib plasma concentration data analysis is not based on a population PK modeling approach.

6. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

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