Official Title:	**Topical Ruxolitinib Evaluation in Vitiligo Study 2 (TRuE-V2): A Phase 3, Double-Blind, Randomized, Vehicle-Controlled, Efficacy and Safety Study of Ruxolitinib Cream Followed by an Extension Period in Participants With Vitiligo**
NCT Number:	NCT04057573
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Clinical Study Protocol

INCB 18424-307

Topical Ruxolitinib Evaluation in Vitiligo Study 2 (TRuE-V2)

A Phase 3, Double-Blind, Randomized, Vehicle-Controlled, Efficacy and Safety Study of Ruxolitinib Cream Followed by an Extension Period in Participants With Vitiligo

Product:	**Ruxolitinib Cream**
IND Number:	**77,101**
EudraCT Number:	**2019-000847-28**
Phase of Study:	**3**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol:	**23 JUN 2019**

INVESTIGATOR'S AGREEMENT

I have read the INCB 18424-307 Protocol (dated 23 JUN 2019) 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

The following abbreviations and special terms are used in this clinical study Protocol.

Abbreviations and Special Terms	Definition
2D	2-dimensional
3D	3-dimensional
AA	alopecia areata
AD	atopic dermatitis
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice daily
BSA	body surface area
CDLQI	Children's Dermatology Life Quality Index
CFR	Code of Federal Regulations
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLQI	Dermatology Life Quality Index
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
EOT	end of treatment
F-BSA	facial body surface area
F-PaGIC-V	facial assessment of Patient Global Impression of Change-Vitiligo
F-PaGVA	facial assessment of Patient's Global Vitiligo Assessment
F-PhGVA	facial assessment of Physician Global Vitiligo Assessment
FSH	follicle-stimulating hormone
F-VASI	Face Vitiligo Area Scoring Index
F-VASI25/50/75/90	≥ 25%/ 50%/ 75%/ 90% improvement from baseline in Face Vitiligo Area Scoring Index score
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	identification

Abbreviations and Special Terms	Definition
IEC	independent ethics committee
IRB	institutional review board
IRT	interactive response technology
ITT	intent to treat
JAK	Janus kinase
LOCF	last observation carry forward
MI	multiple imputation
MMRM	mixed-effect model repeat measurement
NB-UVB	narrow-band ultraviolet B
Pa-GIC-V	Patient Global Impression of Change-Vitiligo
PhGVA	Physician Global Vitiligo Assessment
PK	pharmacokinetic
PP	per protocol
PUVA	psoralen and ultraviolet A
QD	once daily
SAE	serious adverse event
SD	standard deviation
SoA	schedule of assessments
SOP	standard operating procedure
STAT	signal transducer and activator of transcription
SUSAR	suspected unexpected adverse reaction
T-BSA	total body surface area
TCS	topical corticosteroid
TEAE	treatment-emergent adverse event
T-PaGIC-V	total body assessment of Patient Global Impression of Change-Vitiligo
T-PaGVA	total body assessment of Patient's Global Vitiligo Assessment
T-PhGVA	total body assessment of Physician Global Vitiligo Assessment
TSH	thyroid-stimulating hormone
TSQM	Treatment Satisfaction Questionnaire for Medication
T-VASI	total body Vitiligo Area Scoring Index
T-VASI25/50/75/90	≥ 25%/ 50%/ 75%/ 90% improvement in total body Vitiligo Area Scoring Index
TYK	tyrosine kinase
ULN	upper limit of normal
UV	ultraviolet
VASI	Vitiligo Area Scoring Index
VitiQoL	Vitiligo-specific quality of life
VNS	Vitiligo Noticeability Scale

1. PROTOCOL SUMMARY

Protocol Title: A Phase 3, Double-Blind, Randomized, Vehicle-Controlled, Efficacy and Safety Study of Ruxolitinib Cream Followed by an Extension Period in Participants With Vitiligo

Protocol Number: INCB 18424-307

Objectives and Endpoints:

Table 1 presents the primary, key secondary, and selected secondary objectives and endpoints.

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of ruxolitinib cream in participants with vitiligo.	• Proportion of participants achieving F-VASI75 at Week 24.
Key Secondary	
To further assess the efficacy of ruxolitinib cream.	• Percentage change from baseline in F-BSA at Week 24. • Proportion of participants achieving F-VASI50 at Week 24. • Proportion of participants achieving F-VASI75 at Week 52. • Proportion of participants achieving F-VASI90 at Week 24. • Proportion of participants achieving F-VASI90 at Week 52. • Proportion of participants achieving T-VASI50 at Week 24. • Proportion of participants achieving T-VASI50 at Week 52. • Proportion of participants achieving T-VASI75 at Week 52. • Proportion of participants achieving a VNS of "4 – A lot less noticeable" or "5 – No longer noticeable" at Week 24.

Table 1: Primary and Secondary Objectives and Endpoints (Continued)

Objectives	Endpoints
Selected Secondary	
To evaluate the safety and tolerability of ruxolitinib cream.	• The frequency, duration, and severity of AEs; physical examinations; vital signs; and laboratory data for hematology, serum chemistry, and urinalysis.
To further assess the efficacy of ruxolitinib cream.	• Proportion of participants achieving F-VASI25/50/75/90 during the treatment period (double-blind and treatment extension periods). • Proportion of participants achieving T-VASI25/50/75/90 during the treatment period (double-blind and treatment extension periods). • Proportion of participants in each category of VNS during the treatment period (double-blind and treatment extension periods).

Overall Design:

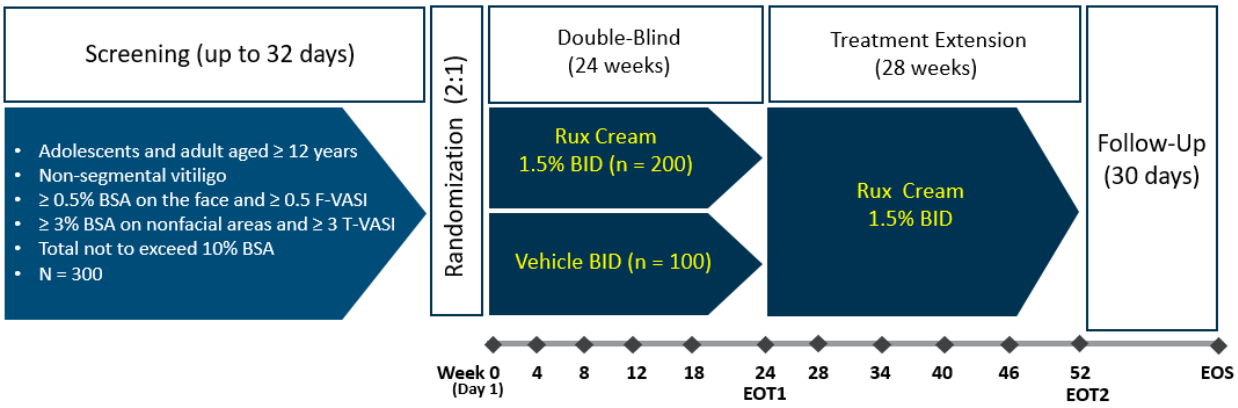
Table 2 presents the key study design elements. Further study details are presented after the table.

Table 2: Key Study Design Elements

Study Phase	Phase 3
Clinical Indication	Vitiligo
Population	Males and females, aged ≥ 12 years, who have vitiligo with ≥ 0.5% BSA on the face, ≥ 0.5 F-VASI, ≥ 3% BSA on nonfacial areas, and ≥ 3 T-VASI. Total body vitiligo area (facial and nonfacial) should not exceed 10% BSA.
Number of Participants	Approximately 300 participants will be randomized 2:1 (ruxolitinib cream 1.5% BID:vehicle).
Study Design	Randomized, double-blind, vehicle-controlled, with a treatment extension period.
Estimated Duration of Study Participation	Screening: Up to 32 days Double-blind period: 24 weeks Treatment extension period: 28 weeks Safety follow-up: 30 days after last application of study medication or last study visit Total: Up to approximately 60 weeks

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

Figure 1: Study Design Schema



This is a randomized, vehicle-controlled study 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) should not exceed 10% BSA. Approximately 300 participants will be randomized 2:1 to receive initial study treatment (ruxolitinib cream 1.5% BID:vehicle; applied to depigmented vitiligo areas on the face and body up to 10% total BSA) for 24 weeks (see Figure 1). Participants will be stratified by age (≤ 40 or > 40 years) and skin type (Fitzpatrick scale Type I and II vs Type III, IV, V, and VI). Adolescents (≥ 12 to < 18 years) will make up at least 10% of the study population, and no more than 50% of participants will be > 40 years old.

After completion of the Week 24 assessments, participants will be offered the opportunity to receive an additional 28 weeks of treatment extension with ruxolitinib cream 1.5% BID. To be eligible for the treatment extension, participants must have completed the baseline and Week 24 visit assessments, be compliant with study procedures, and not have any safety issues. The total treated area should not exceed 10% BSA (facial and nonfacial).

See Section 4.1 for full details of the study design.

Participants who successfully complete the 52-week treatment in this study may be eligible to participate in a separate extension study to evaluate durability of effect and maintenance regimens.

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

Procedure	Screening	Double-Blind, Vehicle Controlled Treatment						Notes
	Days -32 to -1	Day 1	Wk 4 ± 3 d	Wk 8 ± 3 d	Wk 12 ± 3 d	Wk 18 ± 7 d	Wk 24* (EOT1) ± 7 d	*Week 24 is considered the first visit of the treatment extension period.
Administrative procedures								
Informed consent	X							
Contact IRT	X	X	X	X	X	X	X	
Inclusion and exclusion criteria	X	X						
Demography	X							
General and disease medical history	X							
Prior/concomitant medications	X	X	X	X	X	X	X	
Apply study drug		X	X	X	X	X	X*	At each study visit starting at Day 1, the participant should apply the study drug under direct supervision of the site staff. *Not applicable to the EOT1 visit.
Dispense (D) and return (R) study drug and diary cards		D	R/D	R/D	R/D	R/D	R/D*	All tubes of study drug will be weighed before being dispensed. All returned tubes of study drug will be weighed, and those that are unused may be re-dispensed. Re-dispension is not allowed at Week 24. *Dispension is not applicable to the EOT1 visit. At the Week 24 visit, study drug and diary cards are only dispensed to participants continuing in the treatment extension period.
Collect study drug and collect/ review study drug diary cards			X	X	X	X	X	
Assess compliance			X	X	X	X	X	
Safety assessments								
AE assessment	X	X	X	X	X	X	X	Ad hoc photography of skin-related AEs may also occur as applicable.
Targeted physical examinations		X	X	X	X	X		
Comprehensive physical examination	X						X	
Vital signs	X	X	X	X	X	X	X	
12-lead ECG	X							12-lead ECG performed within 2 months before baseline is acceptable.

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

Procedure	Screening	Double-Blind, Vehicle Controlled Treatment						Notes
	Days -32 to -1	Day 1	Wk 4 ± 3 d	Wk 8 ± 3 d	Wk 12 ± 3 d	Wk 18 ± 7 d	Wk 24* (EOT1) ± 7 d	*Week 24 is considered the first visit of the treatment extension period.
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.
F-PhGVA		X			X		X	
T-PhGVA		X			X		X	
Photography of face	X	X*			X		X	2D photography at all sites; 3D photography at selected sites. *If photo quality at screening is not adequate, the photography may be repeated at Day 1. The baseline photos are defined as the adequate ones either taken at screening or Day 1.
Photography of nonfacial target area	X	X*			X		X	2D photography at all sites. The genitalia area should not be photographed. *If photo quality at screening is not adequate, the photography may be repeated at Day 1. The baseline photos are defined as the adequate ones either taken at screening or Day 1.
Patient-reported outcomes								To be evaluated prior to any other study procedures/assessments.
VNS					X		X	The participant will be provided their baseline photo and a mirror to perform this assessment.
Color-matching question					X		X	The participant will be provided their baseline photo and a mirror to perform this assessment.
F-PaGIC-V					X		X	
T-PaGIC-V					X		X	
DLQI		X			X		X	For participants who are age ≥ 12 years to < 16 years at baseline, the CDLQI will be completed instead.
WHO-5		X			X		X	
TSQM					X		X	
VitiQoL		X			X		X	
HADS		X					X	

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

Procedure	Screening	Double-Blind, Vehicle Controlled Treatment						Notes
	Days -32 to -1	Day 1	Wk 4 ± 3 d	Wk 8 ± 3 d	Wk 12 ± 3 d	Wk 18 ± 7 d	Wk 24* (EOT1) ± 7 d	*Week 24 is considered the first visit of the treatment extension period.
Laboratory assessments								
Hematology and chemistry assessments	X	X	X	X*	X	X*	X	*The blood draw at Week 8 and Week 18 is optional for participants who are age < 18 years
Serology and thyroid testing	X							Serology includes HIV antibody.
Urinalysis	X							
FSH	X							For confirmation of nonchildbearing status of women who are postmenopausal defined as having amenorrhea for at least 12 months before screening.
Pregnancy testing	X*	X	X	X	X	X	X	*Female participants of childbearing potential will have a serum test at screening and safety follow-up visits. A urine test will be conducted at all other visits. A positive urine test must be confirmed by a serum test.
PK and translational assessments								
Population-based 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.
Serum sampling for biomarker analysis		X			X		X	

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

Table 4: Schedule of Activities: Treatment Extension Period (Week 28-Week 52)

Procedure	Treatment Extension					Safety Follow-Up	Notes
	Wk 28 ± 7 d	**Wk 34 ± 7 d**	**Wk 40 ± 7 d**	**Wk 46 ± 7 d**	**Wk 52 (EOT2*) ± 7 d**	**30 days + 7 d After EOT1/EOT2** (EOS)**	*EOT2 assessments should be performed in the event a participant's treatment is stopped before Week 52 at any relevant study visit before that time. **After last application of study drug or last visit.
Administrative procedures							
Contact IRT	X	X	X	X	X	X	
Prior/concomitant medications	X	X	X	X	X	X	
Apply study drug	X	X	X	X			At each study visit, the participant should apply the study drug under direct supervision of the site staff.
Dispense (D) and return (R) study drug and diary cards	R/D	R/D	R/D	R/D	R		All tubes of study drug will be weighed before being dispensed. All returned tubes of study drug will be weighed, and those that are unused may be re-dispensed.
Collect study drug and collect/ review study drug diary cards	X	X	X	X	X		
Safety assessments							
AE assessment	X	X	X	X	X	X	
Targeted physical examinations	X	X	X	X		X	
Comprehensive physical examination					X		
Vital signs	X	X	X	X	X	X	
Efficacy assessments							
F-BSA	X	X	X	X	X	X	
T-BSA	X	X	X	X	X	X	Includes facial and nonfacial areas.
F-VASI	X	X	X	X	X	X	
T-VASI	X	X	X	X	X	X	Includes facial and nonfacial areas.
F-PhGVA			X		X		
T-PhGVA			X		X		
Photography of face			X		X		2D photograph at all sites; 3D photography at selected sites.
Photography of nonfacial target area			X		X		2D photography at all sites. The genitalia area should not be photographed.

Table 4: Schedule of Activities: Treatment Extension Period (Week 28-Week 52) (Continued)

Procedure	Treatment Extension					Safety Follow-Up	Notes
	Wk 28 ± 7 d	**Wk 34 ± 7 d**	**Wk 40 ± 7 d**	**Wk 46 ± 7 d**	**Wk 52 (EOT2*) ± 7 d**	**30 days + 7 d After EOT1/EOT2** (EOS)**	*EOT2 assessments should be performed in the event a participant's treatment is stopped before Week 52 at any relevant study visit before that time. **After last application of study drug or last visit.
Patient-reported outcomes							To be evaluated prior to any other study procedures/assessments.
VNS			X		X		The participant will be provided their baseline photo and a mirror to perform this assessment.
Color-matching question			X		X		The participant will be provided their baseline photo and a mirror to perform this assessment.
F-PaGIC-V			X		X		
T-PaGIC-V			X		X		
DLQI			X		X		For participants who are age ≥ 12 years to < 16 years at baseline, the CDLQI will be completed instead.
WHO-5			X		X		
TSQM			X		X		
VitiQoL			X		X		
HADS					X		
Laboratory assessments							
Hematology and chemistry assessments	X	X	X	X*	X	X	*The blood draw at Week 46 is optional for participants who are age < 18 years
Urinalysis							
Pregnancy testing	X	X	X	X	X	X*	*Female participants of childbearing potential will have a serum test at screening and safety follow-up visits. A urine test will be conducted at all other visits. A positive urine test must be confirmed by a serum test.
PK and Translational assessments							
Population-based PK plasma sampling (trough)			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.
Serum sampling for biomarker analysis			X		X		

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

2. INTRODUCTION

Ruxolitinib cream is a topical formulation of ruxolitinib phosphate under development for the treatment of participants with AD, AA, plaque psoriasis, and vitiligo. Ruxolitinib phosphate is an inhibitor of the JAK family of protein TYKs. Inflammatory cytokines are strongly implicated in the pathogenesis of several dermatologic diseases. Because JAKs serve to translate extracellular signals from a number of relevant cytokines and growth factors upregulated in inflammatory diseases such as AD, AA, plaque psoriasis, and vitiligo, JAK inhibitors represent potential therapeutic agents for these disease states.

2.1. Epidemiology of Vitiligo

Vitiligo is an autoimmune pigmentary disease characterized by depigmented patches of skin with a selective loss of melanocytes. It is estimated to affect 0.5% to 2% of the population worldwide (Krüger and Schallreuter 2012). The prevalence is similar between men and women, and there is no known difference in presentation according to skin type or race. Almost 50% of patients present before 20 years of age, and many of them present before 10 years of age (Rodrigues et al 2017). Generalized (non-segmental) vitiligo is the most common type, accounting for up to 90% of cases (Taieb et al 2009). Vitiligo is associated with autoimmune diseases such as Sutton nevus, thyroid disorders, juvenile diabetes mellitus, pernicious anemia, and Addison's disease. 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 a serious disease owing to its substantial psychological impact on patients' day-to-day functioning, and its progressive course if left untreated. Studies have shown that the effect vitiligo has on quality of life, particularly psychological impairment, is similar to other skin diseases, such as psoriasis and AD (Linthorst et al 2009). Involvement of exposed skin, such as the face and hands, can have a major impact on self-esteem and eventually link to the psychological burden and quality of life (Silverberg and Silverberg 2013). In some societies, there is poor acceptance and understanding of the disease, to the extent of discrimination against affected individuals (Yazdani Abyaneh et al 2014). Approximately 75% of vitiligo sufferers feel their appearance is moderately to severely intolerable, and 41% of patients feel that there is little they can do to improve their condition, and feelings of hopelessness increase with time (Salzer and Schallreuter 1995). Not surprisingly, 66% of patients report being distressed by their disease, and 92% have experienced stigmatization (Krüger et al 2014). Feelings of embarrassment and fear of rejection can cause vitiligo patients to withdraw and lead to social isolation in both personal and professional relationships. A majority of patients with vitiligo have reported feelings of anxiety and embarrassment when meeting strangers or beginning a new sexual relationship (Porter et al 1990). Additionally, clinical depression or depressive symptoms are associated with vitiligo. Based on various meta-analyses, patients with vitiligo were approximately 5 times more likely to suffer from depression than healthy controls (Lai et al 2017, Osinubi et al 2018). A recent results of the analysis indicated that the pooled prevalence of depression across 17 unique populations (n = 1711) was 29% (Wang et al 2017).

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. The extent of vitiligo is associated with QOL impairment in children and adolescents, especially self-consciousness, but also bullying and teasing. Teenagers ages 15 to 17 years seem to experience the most self-consciousness of all pediatric age groups (Silverberg and Silverberg 2013). In a study comparing social development and the health-related quality of life of young adult patients with childhood vitiligo with healthy controls, vitiligo patients reporting negative childhood experiences reported significantly more problems in social development than those not reporting negative experiences. Furthermore, negative childhood experiences were significantly associated with more health-related quality of life impairment in early adulthood (Linthorst Homan et al 2008). Thus, vitiligo is considered to be one of the most psychologically devastating diseases in dermatology.

2.2. Current Treatment and Unmet Need in Vitiligo

Currently, there is no approved drug treatment for vitiligo. The conclusions of the most recent updated Cochrane systematic review were hampered by the heterogeneity of the performed clinical studies (Whitton et al 2016). A systemic review on outcomes in a vitiligo study also showed that the 25 different outcomes had been measured in 54 randomized clinical studies. Although repigmentation was measured in 94% of studies, 48 different scales were used to measure it, making comparison among studies impossible (Eleftheriadou et al 2012). Therefore, a definitive clinical recommendation for treatment of vitiligo could not be proposed, and 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 are most useful for treating disease that is localized. Second-line treatments consist of phototherapy (NB-UVB and PUVA) and systemic steroid treatment. Third-line treatments consist of surgical grafting techniques and depigmenting treatments. However, response to current treatment varies, can be time-intensive, can be slow to respond to treatment, and often produces disappointing results if repigmentation is cosmetically unacceptable.

There has been a limited number of randomized controlled clinical studies conducted to adequately support the efficacy of drug treatments in vitiligo. Factors that further limit the evidence for efficacy are variations in study design and outcome measures, small study size (the majority of which included fewer than 50 participants), and deficiencies in methodological quality based on a systematic review of randomized clinical studies evaluating interventions for vitiligo (Whitton et al 2016). Apart from inconclusive (or insufficient) evidence for the efficacy of current off-label drug treatments in vitiligo, their safety profiles may also carry specific restrictions for their topical use. For example, TCS may be associated with local adverse effects, including irreversible ones such as skin atrophy and striae distensae, and an increased susceptibility to skin infections (Coondoo et al 2014). More potent TCS, through their percutaneous absorption and depot-like accumulation in the epidermis, may also produce well-known systemic AEs typical for corticosteroids. Additionally, there are restrictions on the use of such TCS on sensitive skin areas, particularly on the face, and for the overall treatment duration (ie, not to exceed 4 weeks). Therefore, judicious use of high potency preparations of TCS is critical. Topical calcineurin inhibitors are known for the induction of skin burning sensation immediately after their application, which makes their use on the face problematic.

Topical calcineurin inhibitors have been implied in their possible contribution to cutaneous malignancy when used long-term.

Available phototherapy treatments include NB-UVB and PUVA. Phototherapy regimens typically require 2 to 3 treatments per week and long-term duration of treatment. For both NB-UVB and PUVA, 12 to 24 months of continuous phototherapy may be necessary to acquire maximal repigmentation (Taieb et al 2013). A minimum of 6 months of continuous phototherapy is recommended before being considered nonresponsive (Taieb et al 2013, Bae et al 2017). Relapses are common; approximately 60% to 70% of patients resume depigmentation in areas repigmented by treatment within 1 year with PUVA or NB-UVB therapy (Boniface et al 2018). There are also important safety limitations with phototherapy. PUVA carries a risk of phototoxic effects, nausea, and the potential risk for skin cancer. Moreover, PUVA phototherapy is not recommended for children or pregnant women due to risks associated with systemic exposure of psoralen. NB-UVB phototherapy is considered to have safety advantages over PUVA but is also associated with AEs such as erythema, itching, and mild burning or pain (Bae et al 2017). Excimer laser or monochromatic excimer lamp (both at 308 nm) that may reach deeper targets such as amelanotic melanocytes of the hair follicle, and also avoid irradiation of uninvolved skin, may improve clinical outcomes; however, they are limited to localized treatment (Boniface et al 2018).

Lastly, surgical treatments in vitiligo may be considered after failure to respond to drug and light therapies and only for cosmetically sensitive sites where there have been no new vitiligo areas, no Koebner phenomenon, and no extension of the vitiligo area in the previous 12 months. Unsatisfactory cosmetic results and a high incidence of AEs have been reported with certain surgical procedures (Gawkrodger et al 2008, Taieb et al 2013). Surgery is best indicated for stable and localized forms of vitiligo, and only a small number of patients with vitiligo are considered suitable candidates.

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.

2.3. Role of Janus Kinases in Vitiligo

Vitiligo pathogenesis involves intrinsic defects within melanocytes and autoimmunity that targets these cells. Studies have shown that melanocytes from vitiligo patients are more vulnerable than those from healthy individuals (Rodrigues et al 2017, Speeckaert and van Geel 2017). Once melanocytes become stressed, they release inflammatory signals that activate innate immunity, which may represent the initiation event in vitiligo. The oxidative stress, cell damage, and cytokines secreted from innate immune cells then trigger CXCL10 release by skin cells, and that recruits CD8+ T cells to the site. Activated CD8+ T cells produce IFN-γ and other inflammatory mediators to target and destroy melanocytes (Frisoli and Harris 2017). Because IFN-γ signaling utilizes the JAK-STAT pathway, inhibition of JAK signaling may be an effective strategy for vitiligo treatment development.

There are several case reports and case series suggesting that modulation of the immune response through JAK inhibition may be effective in treating vitiligo. A patient with both AA and vitiligo was treated with oral ruxolitinib 20 mg BID for 20 weeks and subsequently had hair regrowth as well as significant repigmentation of areas affected with vitiligo (Harris et al 2016). In another

report, a patient with widespread and progressive vitiligo who did not have a response to topical steroids, tacrolimus ointment, and NB-UVB phototherapy treated with oral tofacitinib at 5 mg QD and resulted in near complete repigmentation after 5 months of treatment (Craiglow and King 2015).

There was a 20-week open-label study using topical ruxolitinib cream (INCB018424) in 12 participants with vitiligo who had a minimum of 1% BSA affected. The results showed a 76% improvement in F-VASI and 26% improvement in T-VASI within 7 of 9 participants who completed the study (Rothstein et al 2017). The same group conducted an additional 32-week extension study with optional NB-UVB treatment (Joshipura et al 2018). Five participants completed the study, and 3 of them received NB-UVB. At Week 52 (Week 20 + Week 32), results showed 92% improvement in F-VASI and 37% in T-VASI. The results also indicated that 2 participants who had failed prior phototherapy and topical INCB18424 cream monotherapy on truncal vitiligo areas responded after combined therapies. Additionally, participants were followed up with at 6 months after treatment discontinuation, and all 5 participants maintained response with maximum duration of more than 40 weeks.

2.4. Ruxolitinib Cream

[redacted]

An oral formulation of ruxolitinib has been clinically evaluated for the treatment of patients with inflammatory disease, myeloproliferative diseases, hematologic malignancies, and solid tumors and is currently approved for the treatment of myelofibrosis and polycythemia vera in multiple countries. In addition to the safety pharmacology and toxicology studies that were completed to support development of ruxolitinib cream, the toxicologic and toxicokinetic profiles of ruxolitinib have also been characterized following oral administration.

[redacted]

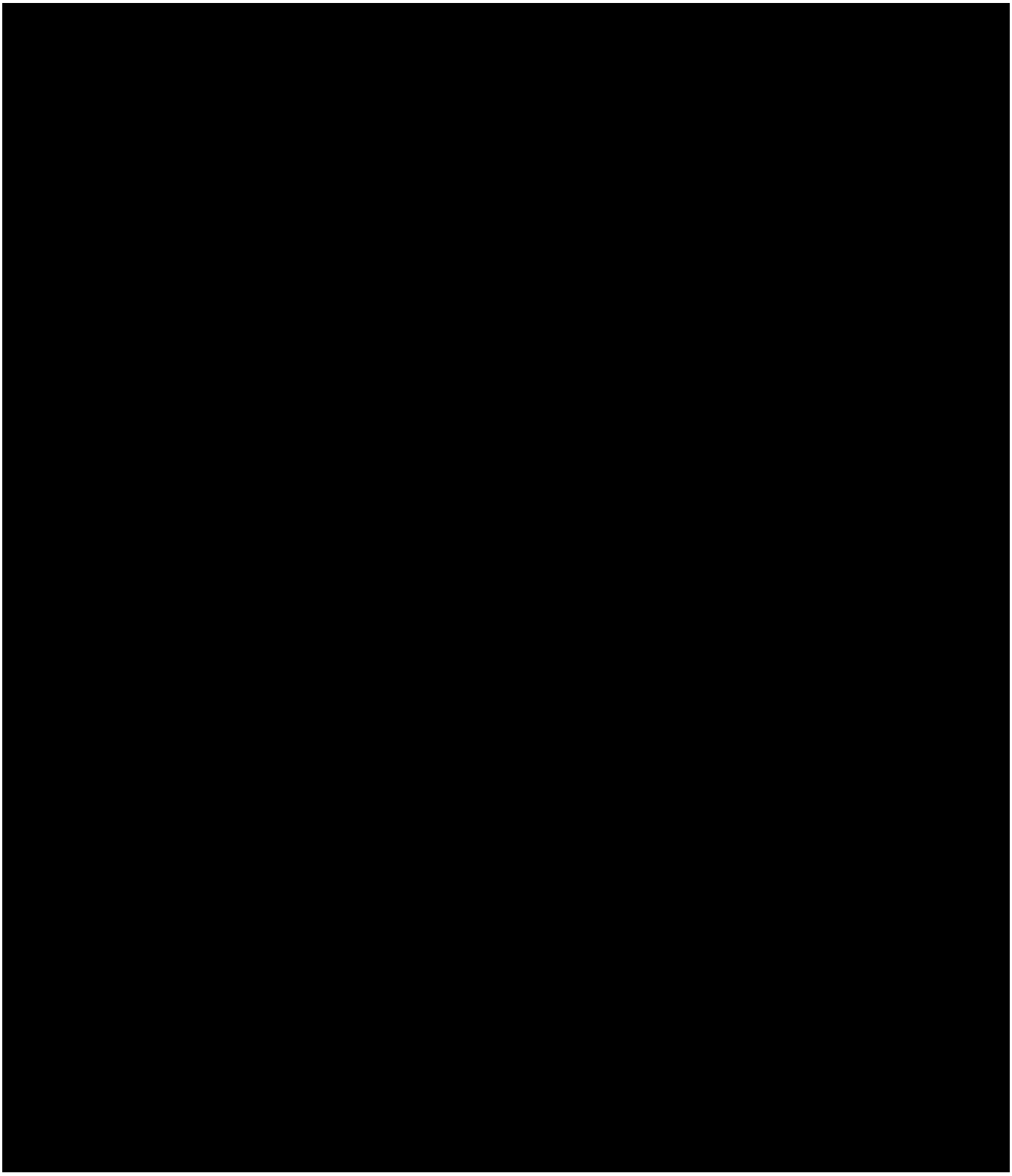
Please refer to the ruxolitinib cream IB.

[redacted]

[redacted]

2.4.2. Clinical Experience

[redacted]



2.4.2.2. Efficacy of Ruxolitinib Cream

2.4.2.2.1. Psoriasis

Ruxolitinib cream has been evaluated in over 200 adults with plaque psoriasis in 3 clinical studies with application of 4 to 12 weeks duration. Overall, ruxolitinib cream (0.5%, 1.0%, or 1.5%) was effective in decreasing disease severity. Observed AEs were mild to moderate in intensity and most were judged unrelated to study medication, with no treatment-related SAEs or withdrawals. Ruxolitinib cream demonstrated to be safe and well-tolerated when applied QD for 12 weeks to plaque psoriasis affecting 2% to 20% of the BSA.

2.4.2.2.2. Atopic Dermatitis

There were 307 adult participants with mild to moderate AD affecting total 3% to 20% BSA enrolled in a Phase 2, randomized, vehicle- and active (triamcinolone 0.1% cream)-controlled dose-ranging study. The mean percentage change from baseline at Week 4 in EASI score demonstrated a significant improvement (1.5% BID [-71.6%0 vs vehicle [-15.5%]). At the highest exposure (1.5% BID), ruxolitinib cream was noninferior to triamcinolone. In addition, significant reductions in itch were noted as early as within a day from the initiation of therapy with ruxolitinib cream. The most frequently reported TEAE was nasopharyngitis, which occurred in 2.0% to 7.8% of participants across dose strengths in the double-blind period and in 5.2% of participants in the open-label period. No fatal or serious TEAEs occurred in participants who received ruxolitinib cream. Phase 3 studies (INCB 18424-303 and -304) in adults and adolescents are ongoing.

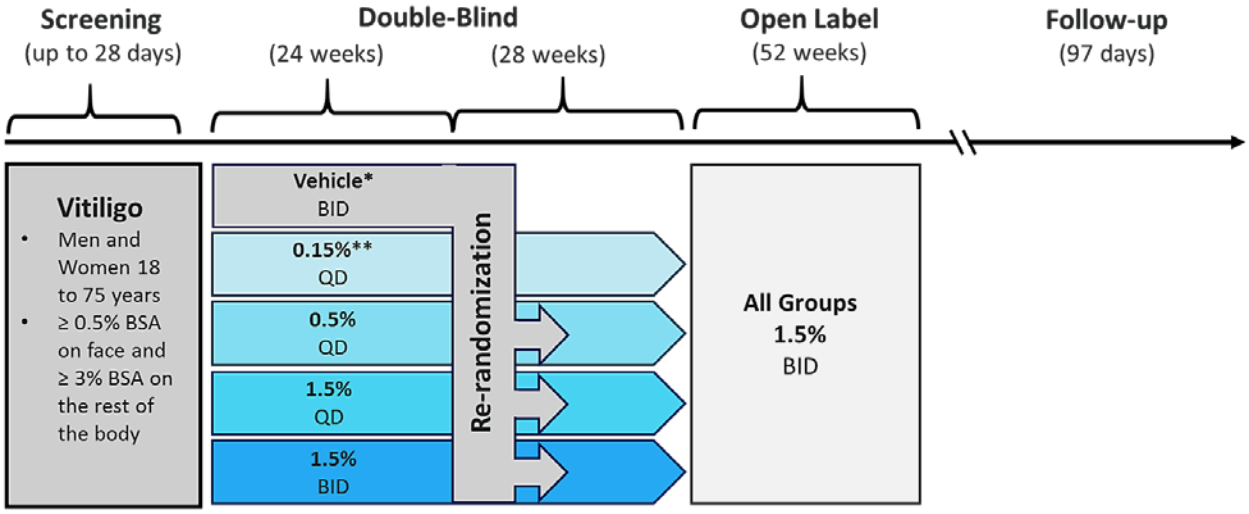
More details are included in the ruxolitinib cream IB.

2.4.2.2.3. Vitiligo

INCB 18424-211 (see Figure 3) is a Phase 2, randomized, double-blind, vehicle-controlled study 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. 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 rerandomized 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.

Figure 3: INCB 18424-211 Study Schema



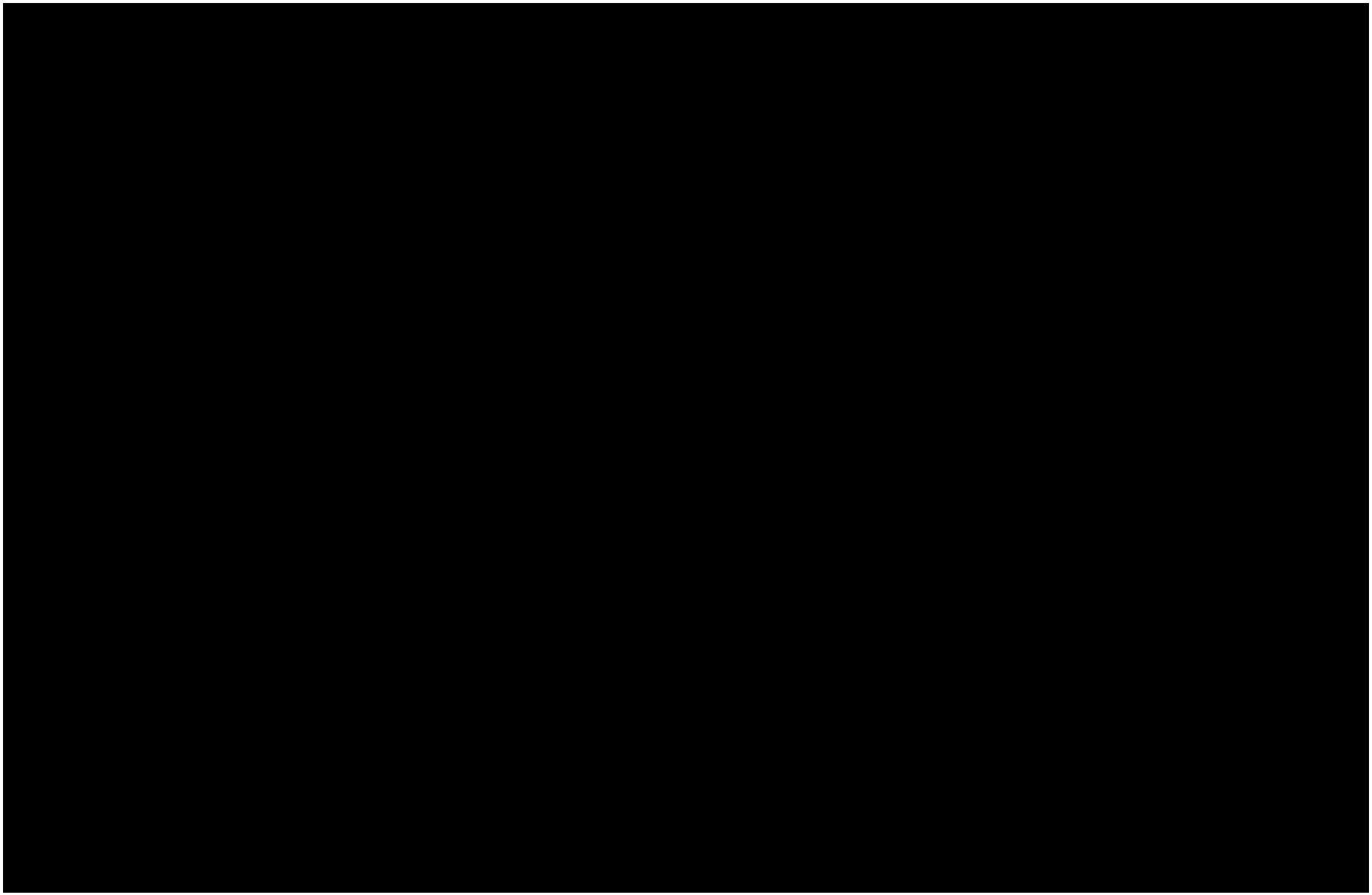
* Re-randomization to 0.5% QD, 1.5% QD or 1.5% BID at Week 24 for vehicle group.
** Re-randomization to 0.5% QD, 1.5% QD or 1.5% BID if < 25% improvement in F-VASI at Week 24 for 0.15% QD group.

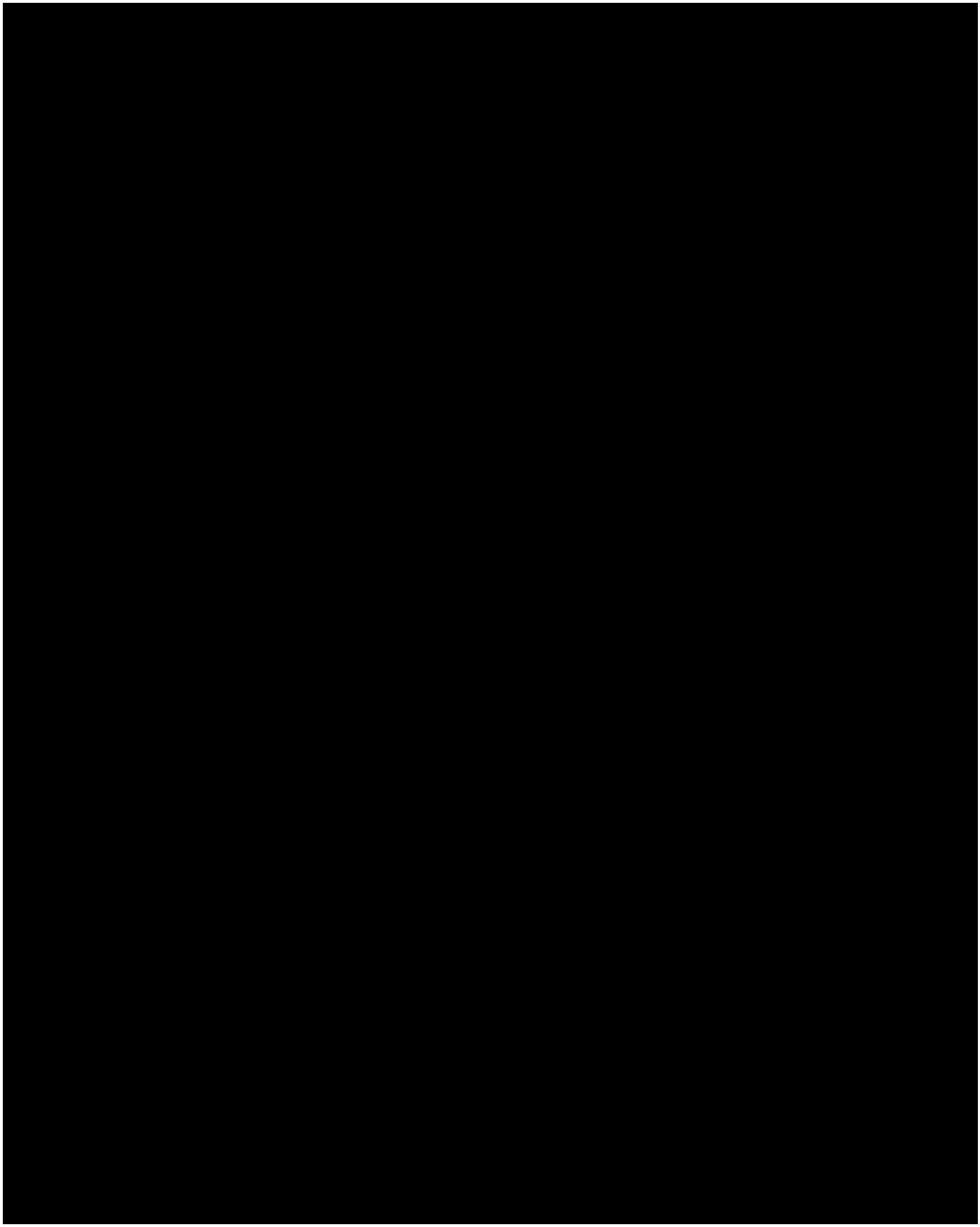
All ruxolitinib treatment arms demonstrated clinically meaningful efficacy and superiority over vehicle. The proportion of participants who achieved an F-VASI50 at Week 24 was statistically significantly greater for ruxolitinib cream versus vehicle with response rates of 32.3%, 25.8%, 50.0%, and 45.5% 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. Participants who were initially randomized to ruxolitinib cream 0.5% QD, 1.5% QD, and 1.5% BID continued on these treatments until Week 52. Continued improvement in F-VASI response in these treatment 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 0.5% QD, 1.5% QD, and 1.5% BID.

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.

Compared with F-VASI, improvement in T-VASI was slower. This observation is not unexpected given that repigmentation on the body and acral areas progresses at a slower rate than facial repigmentation. Despite that, response rates for the F-VASI50, F-VASI75, and T-VASI50 favored the higher strength treatment regimens (both 1.5% QD and 1.5% BID) versus vehicle at Week 24 and 1.5% BID regimen at Week 52 across the endpoints. Given that many participants may not achieve peak response by Week 24 and that there are constraints to the length of the vehicle period, the 1.5% BID regimen appears to have given a higher response over time. Key secondary endpoints including percentage change in F-BSA, F-PhGVA, and PaGIC also followed a similar pattern, with separation from vehicle at Week 24 and continued improvement through Week 52.

All ruxolitinib treatment arms were generally safe and well-tolerated with no significant TEAEs or application site events and no clinically relevant hematological changes. TEAE rate overall is low and similar between active treatment and vehicle treatment. There were 4 SAEs through 52 weeks and all of them were not treatment-related. Discontinuations from treatment through 52 weeks was low. Safety and tolerability were similar between the Week 24 and Week 52 period. [redacted]





[redacted]

[redacted]

3. OBJECTIVES AND ENDPOINTS

Table 8 presents the objectives and endpoints.

Table 8: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of ruxolitinib cream in participants with vitiligo.	• Proportion of participants achieving F-VASI75 at Week 24.
Key Secondary	
To further assess the efficacy of ruxolitinib cream.	• Percentage change from baseline in F-BSA at Week 24. • Proportion of participants achieving F-VASI50 at Week 24. • Proportion of participants achieving F-VASI75 at Week 52. • Proportion of participants achieving F-VASI90 at Week 24. • Proportion of participants achieving F-VASI90 at Week 52. • Proportion of participants achieving T-VASI50 at Week 24. • Proportion of participants achieving T-VASI50 at Week 52. • Proportion of participants achieving T-VASI75 at Week 52. • Proportion of participants achieving a VNS of "4 – A lot less noticeable" or "5 – No longer noticeable" at Week 24.

Table 8: Objectives and Endpoints (Continued)

Objectives	Endpoints
Secondary	
To evaluate the safety and tolerability of ruxolitinib cream.	• The frequency, duration, and severity of AEs; physical examinations; vital signs; and laboratory data for hematology, serum chemistry, and urinalysis.
To further assess the efficacy of ruxolitinib cream.	• Proportion of participants achieving F-VASI25/50/75/90 during the treatment period (double-blind and treatment extension periods). • Percentage change from baseline in F-VASI during the treatment period (double-blind and treatment extension periods). • Percentage change from baseline in F-BSA during the treatment period (double-blind and treatment extension periods). • Percentage change from baseline in T-VASI during the treatment period (double-blind and treatment extension periods). • Percentage change from baseline in T-BSA during the treatment period (double-blind and treatment extension periods). • Proportion of participants achieving T-VASI25/50/75/90 during the treatment period (double-blind and treatment extension periods). • Proportion of participants in each category of VNS during the treatment period (double-blind and treatment extension periods).
To evaluate the ruxolitinib PK in plasma after treatment of ruxolitinib cream.	• Population-based (trough) plasma concentrations of ruxolitinib at Weeks 4, 24 and 40.
Exploratory	
To determine the participants' quality of life.	• Proportion of participants achieving an F-PhGVA of clear (0) or almost clear (1) during the treatment period (double-blind and treatment extension periods). • Proportion of participants achieving an T-PhGVA of clear (0) or almost clear (1) during the treatment period (double-blind and treatment extension periods). • Proportion of participants in each F-PhGVA category during the treatment period (double-blind and treatment extension periods).

Table 8: Objectives and Endpoints (Continued)

Objectives	Endpoints
Exploratory (continued)	
To determine the participants' quality of life. (continued)	• Proportion of participants in each T-PhGVA category during the treatment period (double-blind and treatment extension periods). • Proportion of participants who report F-PaGIC-V of very much improved or much improved during the treatment period (double-blind and treatment extension periods). • Proportion of participants in each F-PaGIC-V category during the treatment period (double-blind and treatment extension periods). • Proportion of participants who report T-PaGIC-V of very much improved or much improved during the treatment period (double-blind and treatment extension periods). • Proportion of participants in each T-PaGIC-V category during the treatment period (double-blind and treatment extension periods). • Proportion of participant in each category for the color-matching question during the treatment period (double-blind and treatment extension periods). • Change from baseline in DLQI (or CDLQI) during the treatment period (double-blind and treatment extension periods). • Change from baseline in WHO-5 during the treatment period (double-blind and treatment extension periods). • Change from baseline in TSQM during the treatment period (double-blind and treatment extension periods). • Change from baseline in VitiQoL during the treatment period (double-blind and treatment extension periods). • Change from baseline in HADS during the treatment period (double-blind and treatment extension periods).
To evaluate translational biomarkers in the blood of participants treated with ruxolitinib cream.	• Change from baseline in the expression of select biomarkers in peripheral blood at Weeks 12, 24, 40, and 52.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, vehicle-controlled study 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, ≥ 3 T-VASI, and for whom total body involved vitiligo area (facial and nonfacial) does not exceed 10% BSA. Approximately 300 participants will be randomized 2:1 to receive initial study treatment (ruxolitinib cream 1.5% BID:vehicle) for 24 weeks (see Figure 1). Participants will be stratified by age (≤ 40 or > 40 years) and skin type (Fitzpatrick scale Type I and II vs Type III, IV, V, and VI). Adolescents (≥ 12 to < 18 years) will make up at least 10% of the study population, and no more than 50% of participants will be > 40 years old.

During the double-blind, vehicle-controlled period, participants will receive ruxolitinib cream 1.5% BID or vehicle for 24 weeks to be applied to depigmented areas only on the face and body up to 10% total BSA. Participants should continue to treat depigmented areas identified for treatment at baseline even if the area begins to improve or fully repigment.

After completion of the Week 24 assessments, participants will be offered the opportunity to continue in the treatment extension period. Participants initially randomized to vehicle will be crossed over to active drug, and participants treated with ruxolitinib cream will receive an additional 28 weeks of treatment with ruxolitinib cream 1.5% BID. To be eligible for the treatment extension, participants must have completed the baseline and Week 24 visit assessments, be compliant with study procedures, and not have any safety issues. During the treatment extension, participants should continue to treat depigmented areas identified for treatment at baseline even if the area begins to improve or fully repigment. Total treated areas (facial and nonfacial areas) should not exceed to 10% BSA.

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

Following the last application of ruxolitinib cream at Week 52, there will be a 30-day safety follow-up period to evaluate safety and duration of response.

Participants who successfully complete the 52-week treatment in this study may be eligible to participate in a separate extension study to evaluate durability of effect and maintenance regimens.

See Section 6.5 for detailed information of study drug modification and application guidance.

4.2. Overall Study Duration

Screening is up to 32 days (~4 weeks); the double-blind, vehicle-controlled treatment period is 24 weeks; the treatment extension period is 28 weeks; and safety follow-up is 30 days. Total duration is up to approximately 60 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 prohibited 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. 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 ≥ 12 months of amenorrhea).
    b. Prepubescent adolescents.
    Note: Information about specific types of acceptable contraceptive measures and duration of contraceptive use are provided in Appendix A.

5. Ability to comprehend and willingness to sign an ICF or written informed consent of the parent(s) or legal guardian and written assent from the 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. 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.

- 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.

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.

5.3. Lifestyle Considerations

Participants should be cautioned 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 wash the treatment areas with mild soap and water and pat dry before application of study drug (see Section 6.6.1).

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

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study treatment. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes that the participant would be eligible if retested. Additionally, a participant who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status or any laboratory abnormality is inconsistent with the participant's medical history. Participants who rescreen must be assigned a new screening number.

5.5. Replacement of Participants

Participants will not be replaced during the study.

6. STUDY TREATMENT

6.1. Study Treatment Application

Table 9 presents the study treatment information.

Table 9: 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:	Double-blind and treatment extension periods: BID. A thin film is applied to depigmented vitiligo areas.	Double-blind period: BID. A thin film is applied to the depigmented vitiligo areas. Treatment extension period: Not applicable.
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 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 study of 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.

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

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

- Participants should apply study drug only 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 even if the area begins to improve or fully repigment.

6.1.2. Application During the Treatment Extension Period

During treatment extension period (Week 24 to Week 52), participants should follow the below study drug application guidance:

- 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 even if the area begins to improve or fully repigment.
- Participants who have an expansion of existing areas of vitiligo during the course of the 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.

6.2. Preparation, Handling, and Accountability

The investigator or designee must confirm 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 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. 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. The system will assign in a 2:1 ratio (ruxolitinib cream 1.5% BID:vehicle), stratified by age (≤ 40 or > 40 years old) and skin type (Fitzpatrick scale Type I and II vs Type III, IV, V, and VI). Adolescents will make up at least 10% or participants, and no more than 50% of participants will be aged greater than 40 years. The IRT will assign participant ID numbers, track participant visits, randomize participants according to the defined parameters, maintain the blinding, and manage study drug inventory. Full details will be provided in the IRT Manual. Study treatment will be dispensed at the study visits summarized in the Schedule of Activities (see Table 3 and Table 4).

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

6.4. Study Treatment Compliance

Compliance with all study-related treatments must be emphasized to the participant by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with ruxolitinib cream 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 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 ruxolitinib cream. Except in cases of emergency, it is recommended that any findings of concern (eg, AE) be confirmed and that the investigator consult with the sponsor medical monitor (or other representative of the sponsor) before interrupting study drug. Additionally, the investigator must obtain approval from the sponsor before restarting study drug. Participants who experience a recurrence of the initial AEs upon restarting the study drug may need the study drug to be permanently discontinued.

Instructions for application interruptions for ruxolitinib cream are outlined in Table 10. Individual decisions regarding interruptions should be made using clinical judgment in consultation with the medical monitor (whenever possible), taking into account relatedness of the AE to the study treatment and the participant's underlying condition.

Table 10: 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 or higher 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 Due to an Adverse Event

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:

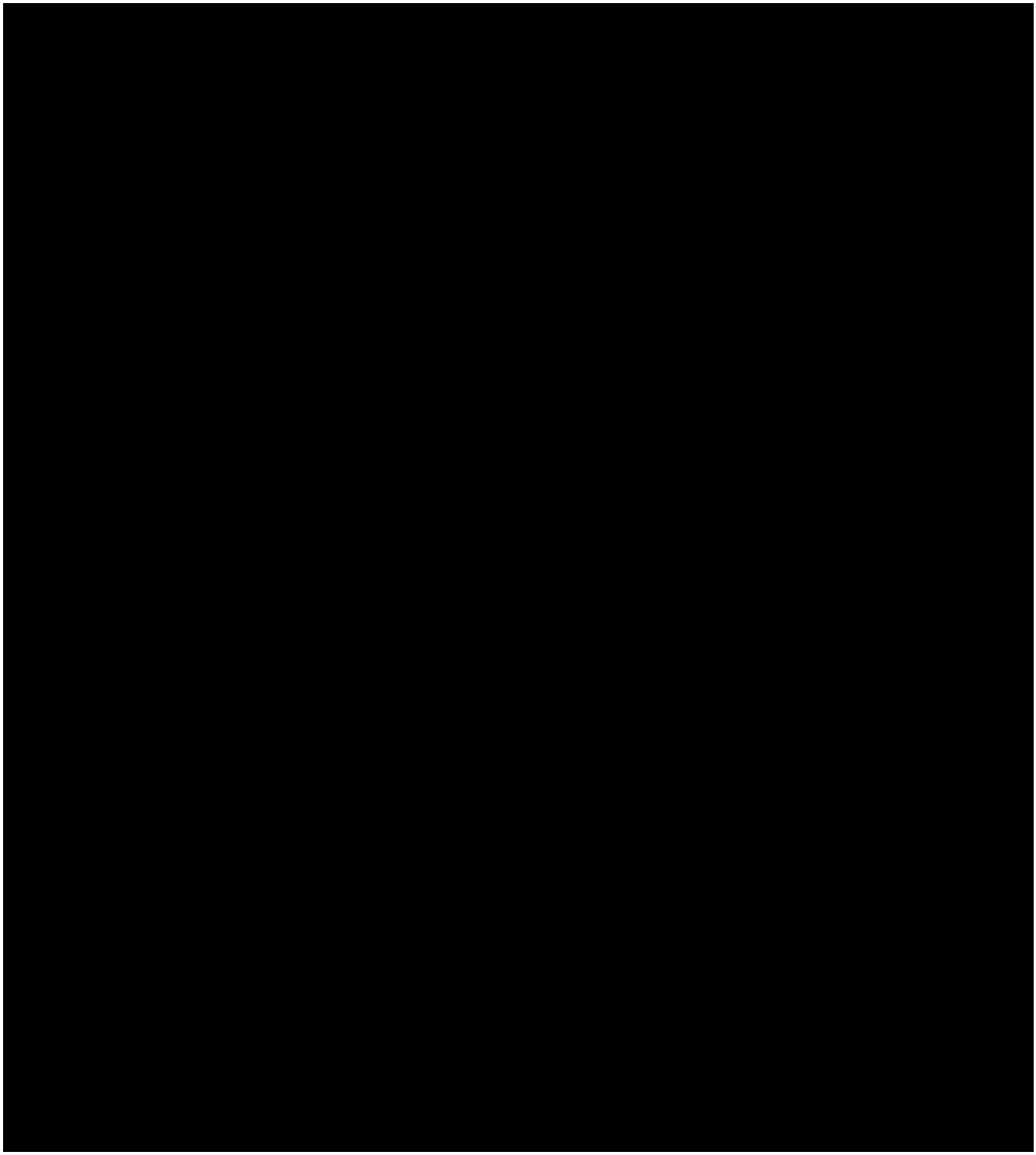
- Occurrence of an AE that is related to treatment with the study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the participant's ability to continue study-specific procedures or continuing treatment is considered to not be in the participant's best interest.
- 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 recorded in the eCRF. Any prior medication received up to 32 days before the first dose of study treatment 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 or prior therapy.



6.8. Treatment After the End of the Study

Participants who successfully complete the 52-week treatment in this study may be eligible to participate in a separate extension study to evaluate durability of effect and maintenance regimens.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

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

- The participant becomes pregnant.
- Consent is withdrawn.

  Note: Consent withdrawn means that the participant has explicitly indicated that they do not want to be followed any longer; in this case no further data, except data in public domain, may be solicited from or collected 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, during the course of the study, a participant is found not to have met eligibility criteria, the medical monitor, in collaboration with the investigator, will determine whether the participant should be withdrawn from study treatment.
- 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 (EOT1 or EOT2 depending on the period during with the participant discontinues treatment). Reasonable efforts should be made to have the participant return for a safety follow-up visit. The last date of the last dose of study drug(s)/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 drug/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 and Table 4 for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. The participant will be counseled regarding the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address

or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, 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

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.
- Participants who are rescreened are required to sign a new ICF.

8.1.2. Screening Procedures

Screening is the interval between signing the ICF and the day that the participant is assigned to the study drug (Day 1). Screening assessments for determination of eligibility may be performed over a period lasting up to 32 days.

Procedures conducted as part of the participant's routine clinical management (eg, clinical laboratory tests) and collected before informed consent is obtained may be used for screening or baseline purposes, provided the procedure meets the Protocol-defined criteria and has been performed within 32 days before Day 1. All information associated with eligibility requirements, including demography and medical history, must be entered into the appropriate eCRF pages.

Results from the screening assessments will be reviewed by the investigators to confirm eligibility before Day 1 and administration of study drug. Tests results that fail eligibility requirements may be repeated once during screening if the investigator believes that the participant would be eligible if retested. For screening assessments that are repeated, the most recent available result before administration of study drug will be used to determine eligibility. See Section 5.4 regarding screen failures.

8.1.3. Interactive Response Technology Procedure

Each participant will be identified in the study by a participant ID number, which is a combination of the site ID and participant number. Site personnel should contact the IRT system to obtain the participant ID number during screening. Upon determining that the participant is eligible for study entry, the IRT system will be contacted to obtain the study 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 Study Reminder Cards and Diaries

Starting at the Day 1 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 Day 1 and at all visits (through Week 52). The reminder card will indicate the date/time of the next visit and will also remind the participant that they should have their application at the clinic during the visit under site supervision after their blood draws for PK and safety evaluations have been completed.

8.1.5. Demography and Medical History

8.1.5.1. Demographics and General Medical History

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

8.1.5.2. Disease Characteristics and Treatment History

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

8.2. Efficacy Assessments

8.2.1. Body Surface Area

Total % BSA (includes facial and nonfacial areas) depigmented by vitiligo will be estimated at each visit. Body surface area assessment will be performed by the Palmar Method. 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).

[redacted]

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

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

The body is divided into the following 6 separate and mutually exclusive sites: (1) head/neck, (2) hands, (3) upper extremities (excluding hands), (4) trunk, (5) lower extremities (excluding feet), and (6) feet. The 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.

8.2.3. Physician's Global Vitiligo Assessment (Facial)

The severity of vitiligo will be assessed by the physician using the PhGVA, which has a 5-point scale (Table 11). Response will be reported for face (F-PhGVA).

Table 11: Facial Physician's Global Vitiligo Assessment Scale

Score	Severity	Description
0	Clear	No signs of vitiligo or complete/near complete repigmentation
1	Almost Clear	Mostly pigmented areas with small depigmented or difficult to repigment areas (eg, philtrum, nares, corners of eyes, perioral skin)
2	Mild Disease	Modest areas of depigmentation (not more than half of facial skin) with approximately 50% pigmentation within vitiligo areas or significant perifollicular pattern present
3	Moderate Disease	Large areas of depigmented vitiligo areas (more than half of facial skin); significant depigmentation within vitiligo areas
4	Severe Disease	Extensive areas of vitiligo to complete depigmentation on face

8.2.4. Physician's Global Vitiligo Assessment (Total Body)

The severity of total body vitiligo will be assessed by the physician using the PhGVA, which has a 5-point scale (Table 12). Response will be reported for total body (T-PhGVA).

Table 12: Total Body Physician's Global Vitiligo Assessment Scale

Score	Severity	Description
0	Clear	No signs of vitiligo or complete/near complete repigmentation
1	Almost Clear	Mostly pigmented areas with small depigmented or difficult to repigment areas (eg, hands, feet, philtrum, nares, corners of eyes, perioral skin)
2	Mild Disease	Modest areas of depigmentation with approximately 50% pigmentation within vitiligo areas or significant perifollicular pattern present
3	Moderate Disease	Large areas of depigmented vitiligo areas; significant depigmentation within vitiligo areas
4	Severe Disease	Extensive areas of vitiligo with complete depigmentation

8.2.5. Photography

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

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

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 and Table 4) using the following tools:

- VNS (Section 8.2.6.1)
- Color-matching question (Section 8.2.6.2)
- F-PaGIC-V (Section 8.2.6.3)
- T-PaGIC-V (Section 8.2.6.4)
- DLQI or CDLQI (Section 8.2.6.5)
- WHO-5 (Section 8.2.6.6)
- TSQM (Section 8.2.6.7)

- VitiQoL (Section 8.2.6.8)
- HADS (Section 8.2.6.9)

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 prior to discussions with the investigator or study site staff.

At the baseline visit, all patient-reported outcomes must be completed before the participant's first study drug application.

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 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.

8.2.6.2. Color-Matching Question

The baseline photograph and current participants' facial image (participants will be provided a mirror) will be shown to the participant for reference, and the participant will be asked to respond to the following query:

> At this point of your treatment, how well does your skin color match between your face treated vitiligo skin and face normal skin? Responses: (1) Excellent, (2) Very good, (3) Good, (4) Poor, and (5) Very poor.

8.2.6.3. Patient Global Impression of Change-Vitiligo (Facial)

The F-PaGIC-V is an assessment of improvement by the participant. It is a 7-point scale comparing the vitiligo areas at baseline with the participant's treated areas of facial vitiligo at the study visit. Response will be reported for face (F-PaGIC-V). The participant will be asked to respond to the following query:

> Since the start of the treatment you've received in this study, your vitiligo on your face treated with the study drug is: (1) Very much improved, (2) Much improved, (3) Minimally improved, (4) No change, (5) Minimally worse, (6) Much worse, and (7) Very much worse.

F-PaGIC-V scores of 1 or 2 can be interpreted as representing treatment success.

8.2.6.4. Patient Global Impression of Change-Vitiligo (Total Body)

The T-PaGIC-V is an assessment of improvement by the participant. It is a 7-point scale comparing the vitiligo areas at baseline with the participant's treated areas of total body vitiligo

at the study visit. Response will be reported for total body (T-PaGIC-V). The participant will be asked to respond to the following query:

> Since the start of the treatment you've received in this study, your vitiligo on your total body treated with the study drug is: (1) Very much improved, (2) Much improved, (3) Minimally improved, (4) No change, (5) Minimally worse, (6) Much worse, and (7) Very much worse.

T-PaGIC-V scores of 1 or 2 can be interpreted as representing treatment success.

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 ≥ 12 years to < 16 years at baseline, the CDLQI will be completed instead of the CDLQI throughout their participation in the 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.

8.2.6.6. WHO-5

The WHO-5 is a validated, self-administered, 5-item questionnaire designed to assess mental well-being over the past 2 weeks, which can be used as an outcome measure for the wanted and unwanted effects of treatments (WHO Collaborating Center for Mental Health, Topp et al 2015). The questionnaire consists of 5 statements, which respondents rate according to the following

scale: 0 = At no time; 1 = Some of the time; 2 = Less than half of the time; 3 = More than half of the time; 4 = Most of the time; 5 = All of the time.

The raw score is calculated by totaling the figures of the 5 answers for a range of 0 to 25, with 0 representing the worst possible and 25 representing the best possible quality of life. A score below 13 indicates poor well-being.

Full details will be provided in the Study Manual.

8.2.6.7. Treatment Satisfaction Questionnaire for Medication

TSQM is a validated 9-item questionnaire that measures a participant's satisfaction with medication taken in a clinical study using a recall period of the past 2 to 3 weeks or since the medication was last used. The questionnaire uses a 7-point scale for each question (Bharmal et al 2009). Full details will be provided in the Study Manual.

8.2.6.8. VitiQoL

VitiQoL is a 15-item quality-of-life assessment that asks participants to rate various aspects of their condition during the past month using a 7-point scale ("Not at all" to "All of the time") (Lilly et al 2013). Full details will be provided in the Study Manual.

8.2.6.9. Hospital Anxiety and Depression Scale

HADS is 14-item questionnaire that assesses the levels of anxiety and depression that a person is currently experiencing (Zigmond and Snaith 1983). There are 7 questions each for measuring anxiety and for measuring depression, with 4 possible responses to each question (responses are scored as 0, 1, 2, or 3). Separate scores are calculated for anxiety and depression. Full details will be provided in the Study Manual.

8.3. Safety Assessments

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

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

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 30 days after the last dose of study 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. Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following-up on AEs that are serious, considered related to the study 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 during the screening process or between visits, or through physical examinations, laboratory tests, or other assessments. The definition, reporting, and recording requirements for AEs are described in Section 9.

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

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

8.3.2. Physical Examinations

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

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

All 12-lead ECGs will be performed with the participant in a recumbent or semi-recumbent position after 5 minutes of rest. Electrocardiograms should be performed as indicated in Table 3. Additional 12-lead ECGs may be performed at other visits as deemed clinically necessary. Twelve-lead ECG performed within 2 months before baseline is acceptable for using as a screening value.

Electrocardiograms will be interpreted by the investigator at the site or designee, and the results will be used for immediate management of the participant's care. There is no central reader of ECGs for this study. The decision to include or exclude a participant or withdraw a participant from the study based on an ECG flagged as "Abnormal, Clinically Significant" is the

responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate. Any abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

8.3.5. Laboratory Assessments

Required laboratory tests are listed in Table 13, which include hematology, chemistry, urinalysis, serology, free T4, TSH, FSH, and pregnancy test (see Table 3 and Table 4). Clinical laboratory tests will be performed at a central laboratory (refer to the Laboratory Manual for sample handling and shipping instructions).

Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. All laboratory tests with values considered clinically significantly abnormal during participation in the study, or within 30 days after the last dose of study 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 13: Required Laboratory Analytes

<table>
<tr><th>Serum Chemistries[a]</th><th>Hematology</th><th>Urinalysis With Microscopic Examination</th><th>Serology</th><th>Other</th></tr>
<tr><td rowspan="3">Albumin
Alkaline phosphatase
ALT
AST
Bicarbonate or CO_2
Blood urea nitrogen or urea
Calcium
Chloride
Creatinine
Glucose
Lactate dehydrogenase
Phosphate
Potassium
Sodium
Total bilirubin
Direct bilirubin (if total bilirubin is elevated above ULN)
Total protein</td><td rowspan="3">Complete blood count, including:
• Hemoglobin
• Hematocrit
• Mean corpuscular volume (MCV)
• Platelet count
• Mean platelet volume
• Red blood cell count
• Reticulocyte count
• White blood cell count

Differential count, including:
• Basophils
• Eosinophils
• Lymphocytes
• Monocytes
• Neutrophils</td><td>Color and appearance
pH and specific gravity
Bilirubin
Glucose
Ketones
Leukocytes
Nitrite
Occult blood
Protein</td><td>HIV antibody</td><td>FSH
Free T4
TSH</td></tr>
<tr><td colspan="3">Pregnancy Testing</td></tr>
<tr><td colspan="3">Female participants of childbearing potential have a serum test at screening and safety follow-up visits. A urine test will be conducted at all other visits. A positive urine test will be confirmed by a serum test.</td></tr>
</table>

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

8.3.5.1. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential during screening and at the safety follow-up visit (30 [+ 7] days after EOT; EOT1 or EOT2 as applicable). Urine pregnancy tests will be conducted as outlined in Table 3 and Table 4, as medically indicated, or per country-specific requirement. Urine pregnancy tests will be performed locally. If a urine pregnancy test is positive, the 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.

8.3.5.2. Serology

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

8.4. Pharmacokinetic Assessments

Venous blood samples will be collected to assess the PK of ruxolitinib cream in this study population 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 during study visits noted in the Table 3. 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.

8.5. Pharmacodynamic and Translational Assessments

Serum will be collected from all participants at all sites for proteomic analysis at timepoints outlined in Table 3 and Table 4. The purpose of this analysis will be to retrospectively evaluate correlative and pharmacodynamic biomarkers of response.

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

8.6. Unscheduled Visits

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

8.7. End of Treatment and/or Early Termination

If a decision is made that the participant will permanently discontinue study drug, then the EOT visit should be conducted (EOT1 or EOT2 depending on the study period when the participant discontinues). If the EOT visit coincides with a regular study visit, then the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT page in the eCRF. If this decision does not coincide with a regular visit, reasonable efforts should be made to have the participant return to the site to have the EOT procedures completed.

8.8. Safety Follow-Up

For participants who do not participate in a separate extension study, the safety follow-up period is the interval between the EOT visit (EOT1 or EOT2 depending on the study period when the participant discontinues) and the scheduled safety follow-up visit, which should occur 30 (+ 7) days after the EOT visit (or after the last dose of study drug/treatment 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/treatment, 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 Meeting the Adverse Event Definition

- Any safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- 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. If present before entering the study, the condition should be captured as medical history. • 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. Conditions that were present at the time informed consent was given should be recorded on the Medical History 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 to sponsor or designee 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 the Adverse Event Form, and the treatment

should be specified on the appropriate eCRF (eg, Prior/Concomitant Medications, Procedures and Non-Drug Therapy).

Assessment of Intensity

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

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

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2:** Moderate; minimal, local, or noninvasive intervention 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 intervention 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 IB and/or Product Information, for marketed products, 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 SAE follow-up 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 within 24 hours of receipt of the information.
- 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) within 24 hours of learning of its occurrence, unless otherwise specified by the Protocol. The investigator will submit any updated SAE data to the sponsor (or designee) within 24 hours of it being available.

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 the event to be reasonably related to the study treatment or study participation, the investigator must notify the sponsor (or designee) within 24 hours of becoming aware of the event.

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

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

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

If an investigator, site personnel performing assessments, or participant is unblinded, the participant must 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 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

Approximately 300 participants will be randomized 2:1 to ruxolitinib cream 1.5% BID or vehicle and stratified by baseline skin type (Fitzpatrick scale Type I and II vs Type III, IV, V, and VI) and age (≤ 40 vs > 40 years). The sample size is calculated to provide sufficient power (> 85%) to detect a difference between the 1.5% BID with the vehicle in primary and key secondary endpoints. The powers for different endpoints are provided in Table 14. The Fisher's exact test with a 2-sided alpha of 0.05 is used to provide a conservative evaluation of statistical power, and it is accurate when there is a small expected number of responders in the vehicle group.

Table 14: Powering for Primary and Key Secondary Endpoints

Endpoints	Response Rates in Ruxolitinib 1.5% BID[a]	Response Rates in Vehicle[a]	Power[b]
F-VASI75 at Week 24	20%	5%	95%
F-VASI50 at Week 24	30%	10%	95%
F-VASI75 at Week 52	30%	10%	95%
F-VASI90 at Week 24	10%	1%	88%
F-VASI90 at Week 52	20%	5%	95%
T-VASI50 at Week 24	10%	1%	88%
T-VASI50 at Week 52	20%	5%	95%
T-VASI75 at Week 52	10%	1%	88%
Vitiligo - VNS Response at Week 24	10%	1%	88%

[a] Based on the results from a Phase 2, randomized, dose-ranging study (INCB18424-211).
[b] Based on the Fisher's exact test with a 2-sided alpha of 0.05.

10.2. Populations for Analysis

The populations for analysis are presented in Table 15.

Table 15: Populations for Analysis

Population	Description
ITT	The ITT population includes all randomized participants. Treatment groups for this population will be defined according to the treatment assignment at randomization.
PP	The PP population includes randomized participants who are considered to be sufficiently compliant with the Protocol.
Safety	The safety population includes all participants who applied at least 1 dose of study drug. Treatment groups for this population will be determined according to the actual treatment the participant received on Day 1.
PK/ pharmacodynamic evaluable	The PK/pharmacodynamic evaluable population includes participants who applied at least 1 dose of ruxolitinib cream and provided at least 1 postdose blood sample for PK. The study pharmacokineticist will review data listings of participant administration and sample records to identify participants to be excluded from the analysis.

10.3. Statistical Analyses

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

The gatekeeping testing strategy for the primary and key secondary analyses will be implemented to control the overall Type I error rate, 2-sided $\alpha = 0.05$. These endpoints will be tested in a fixed sequence at 2-sided $\alpha = 0.05$ level in the following order:

- Proportion of participants achieving F-VASI75 at Week 24
- Percentage change from baseline in F-BSA at Week 24
- Proportion of participants achieving F-VASI50 at Week 24
- Proportion of participants achieving F-VASI75 at Week 52
- Proportion of participants achieving F-VASI90 at Week 24
- Proportion of participants achieving F-VASI90 at Week 52
- Proportion of participants achieving T-VASI50 at Week 24
- Proportion of participants achieving T-VASI50 at Week 52
- Proportion of participants achieving T-VASI75 at Week 52
- Vitiligo - VNS Response at Week 24

10.3.1. Efficacy Analyses

10.3.1.1. Primary Analysis

The primary analysis will be based on the intent-to-treat population. The primary alternative hypothesis (superiority of ruxolitinib cream 1.5% BID compared with vehicle) will be tested using logistic regression. This model will include the treatment group (1.5% BID and vehicle) and stratification factors. The p-value for between-treatment group testing will be calculated based on the Wald test, which will be compared with 0.05. Exact logistic regression (Mehta and Patel 1995) will be used for all of the comparisons if 1.5% BID or vehicle group has an expected cell count less than 5.

The difference in F-VASI75 rates (ruxolitinib cream 1.5% BID vs vehicle) at Week 24 will also be computed. The 95% confidence interval for the difference will be computed based on a large-sample normal approximation with continuity correction. All nonresponders in the double-blind treatment period, as well as all participants who discontinue study treatment at any time before the timepoint of interest, or discontinue from the study for any reason, will be defined as nonresponders for the nonresponder imputation analysis.

Analysis will also be performed in the PP population for the primary endpoint. The following deviations are considered major:

- Lack of informed consent;
- Missing primary endpoints on F-VASI;
- Compliance less than 60% based on the application numbers.

Participants with 1 or more such deviations will be excluded from the PP population. In addition, Protocol deviations related to inclusion/exclusion criteria, discontinuation criteria, and use of excluded concomitant medications will be evaluated and decided whether they should be excluded.

In addition, sensitivity analyses, including MI and LOCF, may be performed. For MI, a fully conditional specification method (van Buuren et al 2007) that assumes the existence of a joint distribution for all variables will be used to impute F-VASI scores. After the missing values are imputed, the binary variables will be derived based on the definition. The imputation will be repeated a number of times to generate corresponding complete data sets, in order to reflect the uncertainty around the true value. Logistic regression will be applied to each imputed dataset, and then the results will be combined for the inference. For LOCF, for the subjects who discontinue study treatment at any time before the timepoint of interest or discontinue from the study for any reason, the last observed nonmissing value will be used to fill in missing values at the timepoint of interest. A tipping point analysis will be conducted to examine the potential effects of missing data. The missing binary response on F-VASI75 at Week 24 in each treatment group will be replaced by a range of values and to see how far we must change them for the results of the study to tip from significant to not. Between-treatment comparisons will be performed using a chi-square test.

Subgroup analysis by baseline character, for example, skin type, age, and region, will be performed. Details will be provided in the Statistical Analysis Plan.

10.3.1.2. Key Secondary Analysis

If the primary objective is achieved, the statistical hypotheses for key secondary endpoints will be tested in the frequency specified in Section 10.3.

Key secondary efficacy analyses at Week 24 will be conducted in the ITT population. The statistical comparisons for binary outcomes (VASI50/90 and VNS response) will be analyzed using the similar method as specified in the primary analysis. For F-BSA, an MMRM will be fitted for the comparisons between INCB018424 1.5% BID and vehicle cream based on percentage change in F-BSA from baseline to Week 24. The MMRM will include the fixed effect of treatment, the randomization stratification factors, the visit, and treatment by visit interaction. The variance-covariance matrix of the within-subject errors in MMRM will be modeled as unstructured. A test for superiority between INCB018424 1.5% BID and vehicle cream will be performed using the least squares mean estimate of the percentage change from baseline in F-BSA at Week 24 from the MMRM specified above. Superiority will be established if the p-value of the difference (INCB018424 1.5% BID minus vehicle) is less than 0.05. ANCOVA (LCOF) models will be fit as sensitivity analysis.

Key secondary endpoints analyses at Week 52 (F-VASI75/90 and T-VASI50/75) will be performed in the ITT population with the following method:

- Patients who discontinue the study drug before Week 24, due to any reason, will be defined as nonresponders for subsequent visits until Week 52.
- For patients who completed Week 24 in Vehicle and 1.5% BID group, missing values of VASI in treatment extension period (including Week 52) will be imputed using linear extrapolation method. The binary outcomes on responses, VASI50/75/90, will be derived based on the imputed values. The statistical comparisons for these endpoints will be analyzed using the similar method as specified in the primary analysis.
- LOCF will also be applied to impute missing data as a sensitivity analysis.

10.3.1.3. Secondary Analysis

All other secondary and exploratory efficacy variables will be summarized using descriptive statistics. For categorical measurements, summary statistics will include sample size, frequency, and percentages. Similar logistic regression models as specified in the primary and key secondary analysis will be used if applicable. For continuous measurements, summary statistics will include sample size, mean, median, SD, standard error of the mean, minimum, and maximum. Continuous efficacy endpoints, including the actual measurement, change from baseline, and percentage change from baseline may also be analyzed by the mixed effect model with repeated measurement.

10.3.2. Safety Analyses

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 tabulated by the MedDRA preferred term and system organ class. Severity of AEs will be based on the National Cancer Institute 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.

The clinical laboratory data will be analyzed using summary statistics; no formal treatment group comparisons are planned. 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 and shift tables relative to baseline will be tabulated.

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. Analysis Plan

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

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

- The Protocol, Protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements, the policies and procedures established by the IRB/IEC, and institutional requirements.
- Any amendments to the Protocol will require 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. 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 designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

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[a]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[a]
  - oral
  - injectable
  - implantable[b]
- Intrauterine device[b]
- Intrauterine hormone-releasing system[b]
- Bilateral tubal occlusion[b]
- Vasectomized partner[bc]
- Sexual abstinence[d]

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

- 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] Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.

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

[c] 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.

[d] 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.

[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 Group 2014.

APPENDIX B. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Not applicable.

Official Title: **Topical Ruxolitinib Evaluation in Vitiligo Study 2 (TRuE-V2): A Phase 3, Double-Blind, Randomized, Vehicle-Controlled, Efficacy and Safety Study of Ruxolitinib Cream Followed by an Extension Period in Participants With Vitiligo**

NCT Number: NCT04057573

Document Date: Clinical Study Protocol Version 4: 13 March 2020

Clinical Study Protocol

INCB 18424-307

Topical Ruxolitinib Evaluation in Vitiligo Study 2
(TRuE-V2)

A Phase 3, Double-Blind, Randomized, Vehicle-Controlled, Efficacy and Safety Study of Ruxolitinib Cream Followed by an Extension Period in Participants With Vitiligo

Product:	**Ruxolitinib Cream**
IND Number:	**77,101**
EudraCT Number:	**2019-000847-28**
Phase of Study:	**3**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol:	**23 JUN 2019**
Amendment 1:	**31 OCT 2019**
Amendment 2:	**12 DEC 2019**
Amendment 3:	**21 FEB 2020**
Amendment 3-US-CA:	**13 MAR 2020**

INVESTIGATOR'S AGREEMENT

I have read the INCB 18424-307 Protocol Amendment 3-US-CA (dated 13 MAR 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

The following abbreviations and special terms are used in this clinical study Protocol.

Abbreviations and Special Terms	Definition
2D	2-dimensional
3D	3-dimensional
AA	alopecia areata
AD	atopic dermatitis
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BID	twice daily
BSA	body surface area
CDLQI	Children's Dermatology Life Quality Index
CFR	Code of Federal Regulations
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLQI	Dermatology Life Quality Index
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
EOT	end of treatment
F-BSA	facial body surface area
F-PaGIC-V	facial assessment of Patient Global Impression of Change-Vitiligo
F-PaGVA	facial assessment of Patient's Global Vitiligo Assessment
F-PhGVA	facial assessment of Physician Global Vitiligo Assessment
FSH	follicle-stimulating hormone
F-VASI	Face Vitiligo Area Scoring Index
F-VASI25/50/75/90	≥ 25%/ 50%/ 75%/ 90% improvement from baseline in Face Vitiligo Area Scoring Index score
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
hCG	human chorionic gonadotrophin

Abbreviations and Special Terms	Definition
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	identification
IEC	independent ethics committee
INFO	International Initiative for Outcomes
IRB	institutional review board
IRT	interactive response technology
ITT	intent to treat
JAK	Janus kinase
LOCF	last observation carry forward
MI	multiple imputation
MMRM	mixed-effect model repeat measurement
NB-UVB	narrow-band ultraviolet B
Pa-GIC-V	Patient Global Impression of Change-Vitiligo
PhGVA	Physician Global Vitiligo Assessment
PK	pharmacokinetic
PP	per protocol
PUVA	psoralen and ultraviolet A
QD	once daily
SAE	serious adverse event
SD	standard deviation
SoA	schedule of assessments
SOP	standard operating procedure
STAT	signal transducer and activator of transcription
SUSAR	suspected unexpected adverse reaction
T-BSA	total body surface area
TCS	topical corticosteroid
TEAE	treatment-emergent adverse event
T-PaGIC-V	total body assessment of Patient Global Impression of Change-Vitiligo
T-PaGVA	total body assessment of Patient's Global Vitiligo Assessment
T-PhGVA	total body assessment of Physician Global Vitiligo Assessment
TSH	thyroid-stimulating hormone
TSQM	Treatment Satisfaction Questionnaire for Medication

Abbreviations and Special Terms	Definition
T-VASI	total body Vitiligo Area Scoring Index
T-VASI25/50/75/90	≥ 25%/ 50%/ 75%/ 90% improvement in total body Vitiligo Area Scoring Index
TYK	tyrosine kinase
ULN	upper limit of normal
UV	ultraviolet
VASI	Vitiligo Area Scoring Index
VitiQoL	Vitiligo-specific quality of life
VNS	Vitiligo Noticeability Scale
WHO-5	World Health Organization-Five Well-Being Index

1. PROTOCOL SUMMARY

Protocol Title: A Phase 3, Double-Blind, Randomized, Vehicle-Controlled, Efficacy and Safety Study of Ruxolitinib Cream Followed by an Extension Period in Participants With Vitiligo

Protocol Number: INCB 18424-307

Objectives and Endpoints:

Table 1 presents the primary, key secondary, and selected secondary objectives and endpoints.

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of ruxolitinib cream in participants with vitiligo.	• Proportion of participants achieving F-VASI75 at Week 24.
Key Secondary	
To further assess the efficacy of ruxolitinib cream.	• Proportion of participants achieving F-VASI50 at Week 24. • Proportion of participants achieving F-VASI90 at Week 24. • Proportion of participants achieving T-VASI50 at Week 24. • Proportion of participants achieving a VNS of "4 – A lot less noticeable" or "5 – No longer noticeable" at Week 24. • Percentage change from baseline in F-BSA at Week 24.
Selected Secondary	
To evaluate the safety and tolerability of ruxolitinib cream.	• The frequency, duration, and severity of AEs; physical examinations; vital signs; and laboratory data for hematology and serum chemistry.
To further assess the efficacy of ruxolitinib cream.	• Proportion of participants achieving F-VASI25/50/75/90 during the treatment period (double-blind and treatment extension periods). • Proportion of participants achieving T-VASI25/50/75/90 during the treatment period (double-blind and treatment extension periods). • Proportion of participants in each category of VNS during the treatment period (double-blind and treatment extension periods).

Overall Design:

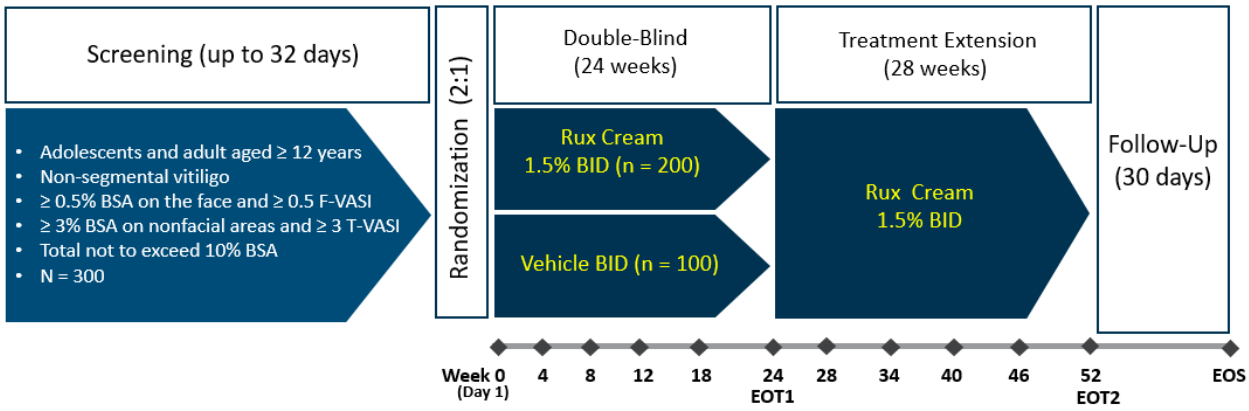
Table 2 presents the key study design elements. Further study details are presented after the table.

Table 2: Key Study Design Elements

Study Phase	Phase 3
Clinical Indication	Vitiligo
Population	Males and females, aged ≥ 12 years, who have vitiligo with ≥ 0.5% BSA on the face, ≥ 0.5 F-VASI, ≥ 3% BSA on nonfacial areas, and ≥ 3 T-VASI. Total body vitiligo area (facial and nonfacial) should not exceed 10% BSA. Participants must have a clinical diagnosis of non-segmental vitiligo. Other forms of vitiligo (eg, segmental) or other differential diagnosis of vitiligo or other skin depigmentation disorders will be excluded. See Section 5 for all inclusion and exclusion criteria.
Number of Participants	Approximately 300 participants will be randomized 2:1 (ruxolitinib cream 1.5% BID:vehicle).
Study Design	Randomized, double-blind, vehicle-controlled, with a treatment extension period. Exit interviews will be conducted with participants at selected sites to better understand their perception of repigmentation improvement and quality of life (see Section 8.1.6).
Estimated Duration of Study Participation	Screening: Up to 32 days Double-blind period: 24 weeks Treatment extension period: 28 weeks Safety follow-up: 30 days after last application of study medication or last study visit Total: Up to approximately 60 weeks
DSMB	The study is not evaluating an endpoint with serious morbidity/mortality. Thus, a DSMB is not required.

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

Figure 1: Study Design Schema



This is a randomized, vehicle-controlled study 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) should not exceed 10% BSA. Approximately 300 participants will be randomized 2:1 to receive initial study treatment (ruxolitinib cream 1.5% BID:vehicle; applied to depigmented vitiligo areas on the face and body up to 10% total BSA) for 24 weeks (see Figure 1). Participants will be stratified by region (North America or Europe) and skin type (Fitzpatrick scale Type I and II vs Type III, IV, V, and VI). Adolescents (≥ 12 to < 18 years) will make up at least 10% of the study population, and no more than 50% of participants will be > 40 years old.

After completion of the Week 24 assessments, participants will be offered the opportunity to receive an additional 28 weeks of treatment extension with ruxolitinib cream 1.5% BID. To be eligible for the treatment extension, participants must have completed the baseline and Week 24 visit assessments, be compliant with study procedures, and not have any safety issues. The total treated area should not exceed 10% BSA (facial and nonfacial).

See Section 4.1 for full details of the study design.

Participants who successfully complete the 52-week treatment in this study may be eligible to participate in a separate extension study to evaluate durability of effect and maintenance regimens.

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

Procedure	Screening	Double-Blind, Vehicle Controlled Treatment						Notes
	Days -32 to -1	Day 1	Wk 4 ± 3 d	Wk 8 ± 3 d	Wk 12 ± 3 d	Wk 18 ± 7 d	Wk 24* (EOT1) ± 7 d	*Week 24 is considered the first visit of the treatment extension period.
Administrative procedures								
Informed consent	X							
Informed consent for optional qualitative exit interviews	X*							A subgroup of participants at sponsor-selected sites will be included in a substudy involving exit interviews. *If consent to provide exit interviews was not obtained at screening, it can be obtained at the participant's next study visit.
Contact IRT	X*	X	X	X	X	X	X	*Entry of age and skin type information into the IRT will be required at screening.
Inclusion and exclusion criteria	X	X						
Demography	X							
General and disease medical history	X							
Prior/concomitant medications	X	X	X	X	X	X	X	
Apply study drug		X	X	X	X	X	X*	At each study visit starting at Day 1, the participant should apply the study drug under direct supervision of the site staff. *Not applicable to the EOT1 visit.
Dispense (D) and return (R) study drug and diary cards		D	R/D	R/D	R/D	R/D	R/D*	All tubes of study drug will be weighed before being dispensed. All returned tubes of study drug will be weighed. *Dispension is not applicable to the EOT1 visit. At the Week 24 visit, study drug and diary cards are only dispensed to participants continuing in the treatment extension period.
Collect study drug and collect/ review study drug diary cards			X	X	X	X	X	
Assess compliance			X	X	X	X	X	
Qualitative exit interview							X*	*The qualitative exit interview is conducted only for the subgroup of participants who consented to participate.

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

Procedure	Screening	Double-Blind, Vehicle Controlled Treatment						Notes
	Days -32 to -1	Day 1	Wk 4 ± 3 d	Wk 8 ± 3 d	Wk 12 ± 3 d	Wk 18 ± 7 d	Wk 24* (EOT1) ± 7 d	*Week 24 is considered the first visit of the treatment extension period.
Safety assessments								
AE assessment	X	X	X	X	X	X	X	Ad hoc photography of skin-related AEs may also occur as applicable.
Targeted physical examinations		X	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.
Comprehensive physical examination	X						X	
Vital signs	X	X	X	X	X	X	X	
12-lead ECG	X							12-lead ECG performed within 2 months before baseline is acceptable.
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.
F-PhGVA		X			X		X	
T-PhGVA		X			X		X	
Photography of face	X	X*			X		X	2D photography at all sites; 3D photography at selected sites. *If photo quality at screening is not adequate, the photography may be repeated at Day 1. The baseline photos are defined as the adequate ones either taken at screening or Day 1.
Photography of nonfacial target area	X	X*			X		X	2D photography at all sites. The genitalia area should not be photographed. *If photo quality at screening is not adequate, the photography may be repeated at Day 1. The baseline photos are defined as the adequate ones either taken at screening or Day 1.

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

Procedure	Screening	Double-Blind, Vehicle Controlled Treatment						Notes
	Days -32 to -1	Day 1	Wk 4 ± 3 d	Wk 8 ± 3 d	Wk 12 ± 3 d	Wk 18 ± 7 d	Wk 24* (EOT1) ± 7 d	*Week 24 is considered the first visit of the treatment extension period.
Patient-reported outcomes								To be evaluated prior to any other study procedures/assessments.
VNS					X		X	The participant will be provided their baseline photo and a mirror to perform this assessment.
Color-matching question					X		X	The participant will be provided their baseline photo and a mirror to perform this assessment.
F-PaGIC-V					X		X	
T-PaGIC-V					X		X	
DLQI		X			X		X	For participants who are age ≥ 12 years to < 16 years at baseline, the CDLQI will be completed instead.
WHO-5		X			X		X	
TSQM					X		X	
VitiQoL		X			X		X	
HADS		X					X	
Laboratory assessments								
Hematology and chemistry assessments	X	X	X	X*	X	X*	X	*The blood draw at Week 8 and Week 18 is optional for participants who are age < 18 years
Serology and thyroid testing	X							Serology includes HIV antibody.
Urinalysis	X							
FSH	X							For confirmation of nonchildbearing status of women who are postmenopausal defined as having amenorrhea for at least 12 months without an alternative medical cause before screening.
Pregnancy testing	X*	X	X	X	X	X	X	*Female participants of childbearing potential will have a serum test at screening and safety follow-up visits. A urine test will be conducted at all other visits. A positive urine test must be confirmed by a serum test.
PK and translational assessments								
Population-based 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.
Serum sampling for biomarker analysis		X			X		X	

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

Table 4: Schedule of Activities: Treatment Extension Period (Week 28-Week 52)

Procedure	Treatment Extension					Safety Follow-Up	Notes
	Wk 28 ± 7 d	**Wk 34 ± 7 d**	**Wk 40 ± 7 d**	**Wk 46 ± 7 d**	**Wk 52 (EOT2*) ± 7 d**	**30 days + 7 d After EOT1/EOT2** (EOS)**	*EOT2 assessments should be performed in the event a participant's treatment is stopped before Week 52 at any relevant study visit before that time. **After last application of study drug or last visit.
Administrative procedures							
Contact IRT	X	X	X	X	X	X	
Prior/concomitant medications	X	X	X	X	X	X	
Apply study drug	X	X	X	X			At each study visit, the participant should apply the study drug under direct supervision of the site staff.
Dispense (D) and return (R) study drug and diary cards	R/D	R/D	R/D	R/D	R		All tubes of study drug will be weighed before being dispensed. All returned tubes of study drug will be weighed.
Collect study drug and collect/ review study drug diary cards	X	X	X	X	X		
Assess compliance	X	X	X	X	X		
Qualitative exit interview					X*		*The qualitative exit interview is conducted only for the subgroup of participants who consented to participate.
Safety assessments							
AE assessment	X	X	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.
Targeted physical examinations	X	X	X	X		X	
Comprehensive physical examination					X		
Vital signs	X	X	X	X	X	X	
Efficacy assessments							
F-BSA	X	X	X	X	X	X	
T-BSA	X	X	X	X	X	X	Includes facial and nonfacial areas.
F-VASI	X	X	X	X	X	X	
T-VASI	X	X	X	X	X	X	Includes facial and nonfacial areas.
F-PhGVA			X		X		

Table 4: Schedule of Activities: Treatment Extension Period (Week 28-Week 52) (Continued)

Procedure	Treatment Extension					Safety Follow-Up	Notes
	Wk 28 ± 7 d	**Wk 34 ± 7 d**	**Wk 40 ± 7 d**	**Wk 46 ± 7 d**	**Wk 52 (EOT2*) ± 7 d**	**30 days + 7 d After EOT1/EOT2** (EOS)**	*EOT2 assessments should be performed in the event a participant's treatment is stopped before Week 52 at any relevant study visit before that time. **After last application of study drug or last visit.
T-PhGVA			X		X		
Photography of face			X		X		2D photograph at all sites; 3D photography at selected sites.
Photography of nonfacial target area			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		The participant will be provided their baseline photo and a mirror to perform this assessment.
Color-matching question			X		X		The participant will be provided their baseline photo and a mirror to perform this assessment.
F-PaGIC-V			X		X		
T-PaGIC-V			X		X		
DLQI			X		X		For participants who are age ≥ 12 years to < 16 years at baseline, the CDLQI will be completed instead.
WHO-5			X		X		
TSQM			X		X		
VitiQoL			X		X		
HADS					X		
Laboratory assessments							
Hematology and chemistry assessments	X	X	X	X*	X	X	*The blood draw at Week 46 is optional for participants who are age < 18 years
Pregnancy testing	X	X	X	X	X	X*	*Female participants of childbearing potential will have a serum test at screening and safety follow-up visits. A urine test will be conducted at all other visits. A positive urine test must be confirmed by a serum test.

Table 4: Schedule of Activities: Treatment Extension Period (Week 28-Week 52) (Continued)

Procedure	Treatment Extension					Safety Follow-Up	Notes
	Wk 28 ± 7 d	**Wk 34 ± 7 d**	**Wk 40 ± 7 d**	**Wk 46 ± 7 d**	**Wk 52 (EOT2*) ± 7 d**	**30 days + 7 d After EOT1/EOT2** (EOS)**	*EOT2 assessments should be performed in the event a participant's treatment is stopped before Week 52 at any relevant study visit before that time. **After last application of study drug or last visit.
PK and Translational assessments							
Population-based PK plasma sampling (trough)			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.
Serum sampling for biomarker analysis			X		X		

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

2. INTRODUCTION

Ruxolitinib cream is a topical formulation of ruxolitinib phosphate under development for the treatment of participants with AD, AA, plaque psoriasis, and vitiligo. Ruxolitinib phosphate is an inhibitor of the JAK family of protein TYKs. Inflammatory cytokines are strongly implicated in the pathogenesis of several dermatologic diseases. Because JAKs serve to translate extracellular signals from a number of relevant cytokines and growth factors upregulated in inflammatory diseases such as AD, AA, plaque psoriasis, and vitiligo, JAK inhibitors represent potential therapeutic agents for these disease states.

2.1. Epidemiology of Vitiligo

Vitiligo is an autoimmune pigmentary disease characterized by depigmented patches of skin with a selective loss of melanocytes. It is estimated to affect 0.5% to 2% of the population worldwide (Krüger and Schallreuter 2012). The prevalence is similar between men and women, and there is no known difference in presentation according to skin type or race. Almost 50% of patients present before 20 years of age, and many of them present before 10 years of age (Rodrigues et al 2017). Generalized (non-segmental) vitiligo is the most common type, accounting for up to 90% of cases (Taieb et al 2009). Vitiligo is associated with autoimmune diseases such as Sutton nevus, thyroid disorders, juvenile diabetes mellitus, pernicious anemia, and Addison's disease. 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 a serious disease owing to its substantial psychological impact on patients' day-to-day functioning, and its progressive course if left untreated. Studies have shown that the effect vitiligo has on quality of life, particularly psychological impairment, is similar to other skin diseases, such as psoriasis and AD (Linthorst et al 2009). Involvement of exposed skin, such as the face and hands, can have a major impact on self-esteem and eventually link to the psychological burden and quality of life (Silverberg and Silverberg 2013). In some societies, there is poor acceptance and understanding of the disease, to the extent of discrimination against affected individuals (Yazdani Abyaneh et al 2014). Approximately 75% of vitiligo sufferers feel their appearance is moderately to severely intolerable, and 41% of patients feel that there is little they can do to improve their condition, and feelings of hopelessness increase with time (Salzer and Schallreuter 1995). Not surprisingly, 66% of patients report being distressed by their disease, and 92% have experienced stigmatization (Krüger et al 2014). Feelings of embarrassment and fear of rejection can cause vitiligo patients to withdraw and lead to social isolation in both personal and professional relationships. A majority of patients with vitiligo have reported feelings of anxiety and embarrassment when meeting strangers or beginning a new sexual relationship (Porter et al 1990). Additionally, clinical depression or depressive symptoms are associated with vitiligo. Based on various meta-analyses, patients with vitiligo were approximately 5 times more likely to suffer from depression than healthy controls (Lai et al 2017, Osinubi et al 2018). A recent results of the analysis indicated that the pooled prevalence of depression across 17 unique populations (n = 1711) was 29% (Wang et al 2017).

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. The extent of vitiligo is associated with QOL impairment in children and adolescents, especially self-consciousness, but also bullying and teasing. Teenagers ages 15 to 17 years seem to experience the most self-consciousness of all pediatric age groups (Silverberg and Silverberg 2013). In a study comparing social development and the health-related quality of life of young adult patients with childhood vitiligo with healthy controls, vitiligo patients reporting negative childhood experiences reported significantly more problems in social development than those not reporting negative experiences. Furthermore, negative childhood experiences were significantly associated with more health-related quality of life impairment in early adulthood (Linthorst Homan et al 2008). Thus, vitiligo is considered to be one of the most psychologically devastating diseases in dermatology.

2.2. Current Treatment and Unmet Need in Vitiligo

Currently, there is no approved drug treatment for vitiligo. The conclusions of the most recent updated Cochrane systematic review were hampered by the heterogeneity of the performed clinical studies (Whitton et al 2016). A systemic review on outcomes in a vitiligo study also showed that the 25 different outcomes had been measured in 54 randomized clinical studies. Although repigmentation was measured in 94% of studies, 48 different scales were used to measure it, making comparison among studies impossible (Eleftheriadou et al 2012). Therefore, a definitive clinical recommendation for treatment of vitiligo could not be proposed, and 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 are most useful for treating disease that is localized. Second-line treatments consist of phototherapy (NB-UVB and PUVA) and systemic steroid treatment. Third-line treatments consist of surgical grafting techniques and depigmenting treatments. However, response to current treatment varies, can be time-intensive, can be slow to respond to treatment, and often produces disappointing results if repigmentation is cosmetically unacceptable.

There has been a limited number of randomized controlled clinical studies conducted to adequately support the efficacy of drug treatments in vitiligo. Factors that further limit the evidence for efficacy are variations in study design and outcome measures, small study size (the majority of which included fewer than 50 participants), and deficiencies in methodological quality based on a systematic review of randomized clinical studies evaluating interventions for vitiligo (Whitton et al 2016). Apart from inconclusive (or insufficient) evidence for the efficacy of current off-label drug treatments in vitiligo, their safety profiles may also carry specific restrictions for their topical use. For example, TCS may be associated with local adverse effects, including irreversible ones such as skin atrophy and striae distensae, and an increased susceptibility to skin infections (Coondoo et al 2014). More potent TCS, through their percutaneous absorption and depot-like accumulation in the epidermis, may also produce well-known systemic AEs typical for corticosteroids. Additionally, there are restrictions on the use of such TCS on sensitive skin areas, particularly on the face, and for the overall treatment duration (ie, not to exceed 4 weeks). Therefore, judicious use of high potency preparations of TCS is critical. Topical calcineurin inhibitors are known for the induction of skin burning sensation immediately after their application, which makes their use on the face problematic.

Topical calcineurin inhibitors have been implied in their possible contribution to cutaneous malignancy when used long-term.

Available phototherapy treatments include NB-UVB and PUVA. Phototherapy regimens typically require 2 to 3 treatments per week and long-term duration of treatment. For both NB-UVB and PUVA, 12 to 24 months of continuous phototherapy may be necessary to acquire maximal repigmentation (Taieb et al 2013). A minimum of 6 months of continuous phototherapy is recommended before being considered nonresponsive (Taieb et al 2013, Bae et al 2017). Relapses are common; approximately 60% to 70% of patients resume depigmentation in areas repigmented by treatment within 1 year with PUVA or NB-UVB therapy (Boniface et al 2018). There are also important safety limitations with phototherapy. PUVA carries a risk of phototoxic effects, nausea, and the potential risk for skin cancer. Moreover, PUVA phototherapy is not recommended for children or pregnant women due to risks associated with systemic exposure of psoralen. NB-UVB phototherapy is considered to have safety advantages over PUVA but is also associated with AEs such as erythema, itching, and mild burning or pain (Bae et al 2017). Excimer laser or monochromatic excimer lamp (both at 308 nm) that may reach deeper targets such as amelanotic melanocytes of the hair follicle, and also avoid irradiation of uninvolved skin, may improve clinical outcomes; however, they are limited to localized treatment (Boniface et al 2018).

Lastly, surgical treatments in vitiligo may be considered after failure to respond to drug and light therapies and only for cosmetically sensitive sites where there have been no new vitiligo areas, no Koebner phenomenon, and no extension of the vitiligo area in the previous 12 months. Unsatisfactory cosmetic results and a high incidence of AEs have been reported with certain surgical procedures (Gawkrodger et al 2008, Taieb et al 2013). Surgery is best indicated for stable and localized forms of vitiligo, and only a small number of patients with vitiligo are considered suitable candidates.

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.

2.3. Role of Janus Kinases in Vitiligo

Vitiligo pathogenesis involves intrinsic defects within melanocytes and autoimmunity that targets these cells. Studies have shown that melanocytes from vitiligo patients are more vulnerable than those from healthy individuals (Rodrigues et al 2017, Speeckaert and van Geel 2017). Once melanocytes become stressed, they release inflammatory signals that activate innate immunity, which may represent the initiation event in vitiligo. The oxidative stress, cell damage, and cytokines secreted from innate immune cells then trigger CXCL10 release by skin cells, and that recruits CD8+ T cells to the site. Activated CD8+ T cells produce IFN-γ and other inflammatory mediators to target and destroy melanocytes (Frisoli and Harris 2017). Because IFN-γ signaling utilizes the JAK-STAT pathway, inhibition of JAK signaling may be an effective strategy for vitiligo treatment development.

There are several case reports and case series suggesting that modulation of the immune response through JAK inhibition may be effective in treating vitiligo. A patient with both AA and vitiligo was treated with oral ruxolitinib 20 mg BID for 20 weeks and subsequently had hair regrowth as well as significant repigmentation of areas affected with vitiligo (Harris et al 2016). In another

report, a patient with widespread and progressive vitiligo who did not have a response to topical steroids, tacrolimus ointment, and NB-UVB phototherapy treated with oral tofacitinib at 5 mg QD and resulted in near complete repigmentation after 5 months of treatment (Craiglow and King 2015).

There was a 20-week open-label study using topical ruxolitinib cream (INCB018424) in 12 participants with vitiligo who had a minimum of 1% BSA affected. The results showed a 76% improvement in F-VASI and 26% improvement in T-VASI within 7 of 9 participants who completed the study (Rothstein et al 2017). The same group conducted an additional 32-week extension study with optional NB-UVB treatment (Joshipura et al 2018). Five participants completed the study, and 3 of them received NB-UVB. At Week 52 (Week 20 + Week 32), results showed 92% improvement in F-VASI and 37% in T-VASI. The results also indicated that 2 participants who had failed prior phototherapy and topical INCB18424 cream monotherapy on truncal vitiligo areas responded after combined therapies. Additionally, participants were followed up with at 6 months after treatment discontinuation, and all 5 participants maintained response with maximum duration of more than 40 weeks.

2.4. Ruxolitinib Cream

[redacted]

An oral formulation of ruxolitinib has been clinically evaluated for the treatment of patients with inflammatory disease, myeloproliferative diseases, hematologic malignancies, and solid tumors and is currently approved for the treatment of myelofibrosis and polycythemia vera in multiple countries. In addition to the safety pharmacology and toxicology studies that were completed to support development of ruxolitinib cream, the toxicologic and toxicokinetic profiles of ruxolitinib have also been characterized following oral administration.

[redacted]

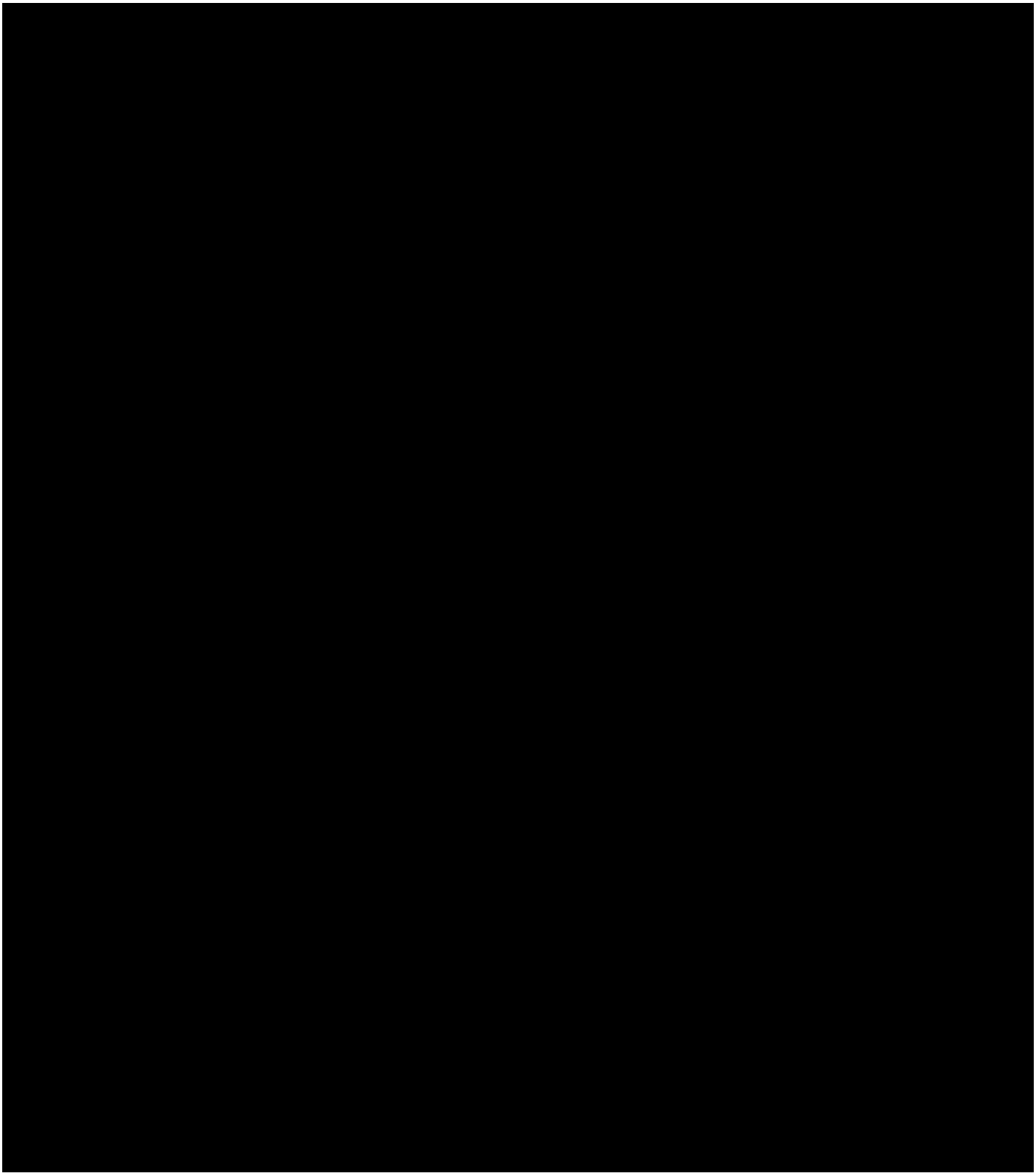
Please refer to the ruxolitinib cream IB.

[redacted]

[redacted]

2.4.2. Clinical Experience

[redacted]



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2.4.2.2. Efficacy of Ruxolitinib Cream

2.4.2.2.1. Psoriasis

Ruxolitinib cream has been evaluated in over 200 adults with plaque psoriasis in 3 clinical studies with application of 4 to 12 weeks duration. Overall, ruxolitinib cream (0.5%, 1.0%, or 1.5%) was effective in decreasing disease severity. Observed AEs were mild to moderate in intensity and most were judged unrelated to study medication, with no treatment-related SAEs or withdrawals. Ruxolitinib cream demonstrated to be safe and well-tolerated when applied QD for 12 weeks to plaque psoriasis affecting 2% to 20% of the BSA.

2.4.2.2.2. Atopic Dermatitis

There were 307 adult participants with mild to moderate AD affecting total 3% to 20% BSA enrolled in a Phase 2, randomized, vehicle- and active (triamcinolone 0.1% cream)-controlled dose-ranging study. The mean percentage change from baseline at Week 4 in EASI score demonstrated a significant improvement (1.5% BID [-71.6%0 vs vehicle [-15.5%]). At the highest exposure (1.5% BID), ruxolitinib cream was noninferior to triamcinolone. In addition, significant reductions in itch were noted as early as within a day from the initiation of therapy with ruxolitinib cream. The most frequently reported TEAE was nasopharyngitis, which occurred in 2.0% to 7.8% of participants across dose strengths in the double-blind period and in 5.2% of participants in the open-label period. No fatal or serious TEAEs occurred in participants who received ruxolitinib cream. Phase 3 studies (INCB 18424-303 and -304) in adults and adolescents are ongoing.

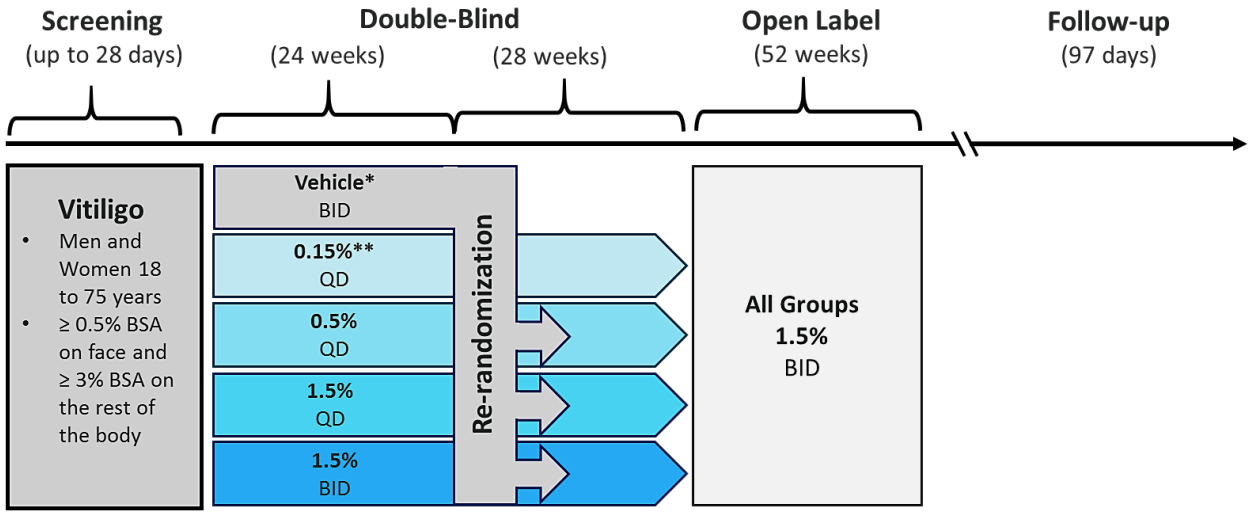
More details are included in the ruxolitinib cream IB.

2.4.2.2.3. Vitiligo

INCB 18424-211 (see Figure 3) is a Phase 2, randomized, double-blind, vehicle-controlled study 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. 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 rerandomized 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.

Figure 3: INCB 18424-211 Study Schema



* Re-randomization to 0.5% QD, 1.5% QD or 1.5% BID at Week 24 for vehicle group.
** Re-randomization to 0.5% QD, 1.5% QD or 1.5% BID if < 25% improvement in F-VASI at Week 24 for 0.15% QD group.

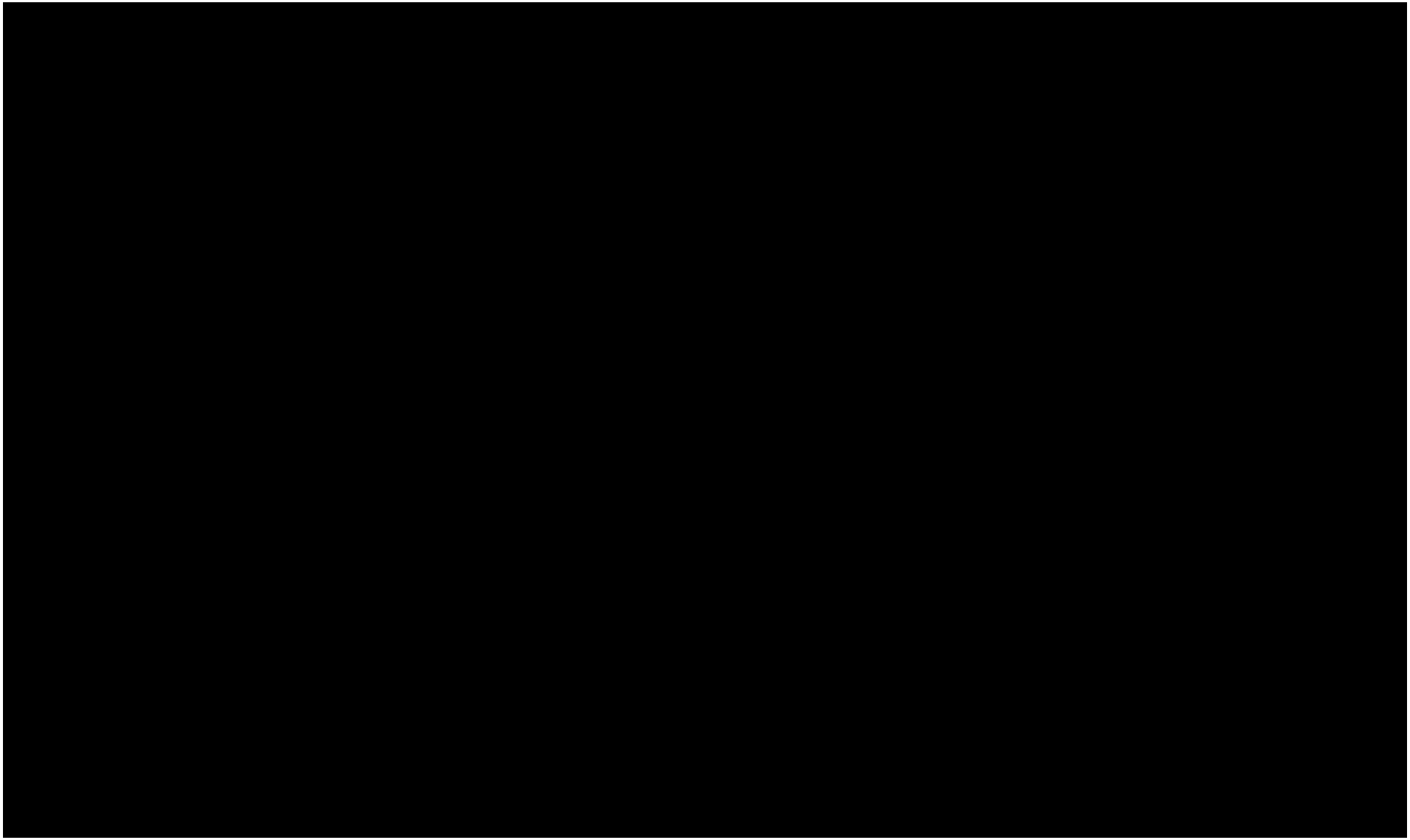
All ruxolitinib treatment arms demonstrated clinically meaningful efficacy and superiority over vehicle. The proportion of participants who achieved an F-VASI50 at Week 24 was statistically significantly greater for ruxolitinib cream versus vehicle with response rates of 32.3%, 25.8%, 50.0%, and 45.5% 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. Participants who were initially randomized to ruxolitinib cream 0.5% QD, 1.5% QD, and 1.5% BID continued on these treatments until Week 52. Continued improvement in F-VASI response in these treatment 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 0.5% QD, 1.5% QD, and 1.5% BID. Large effect size (Cohen's D = 1.14) is observed based on percentage change from baseline between ruxolitinib cream 1.5%BID and vehicle.

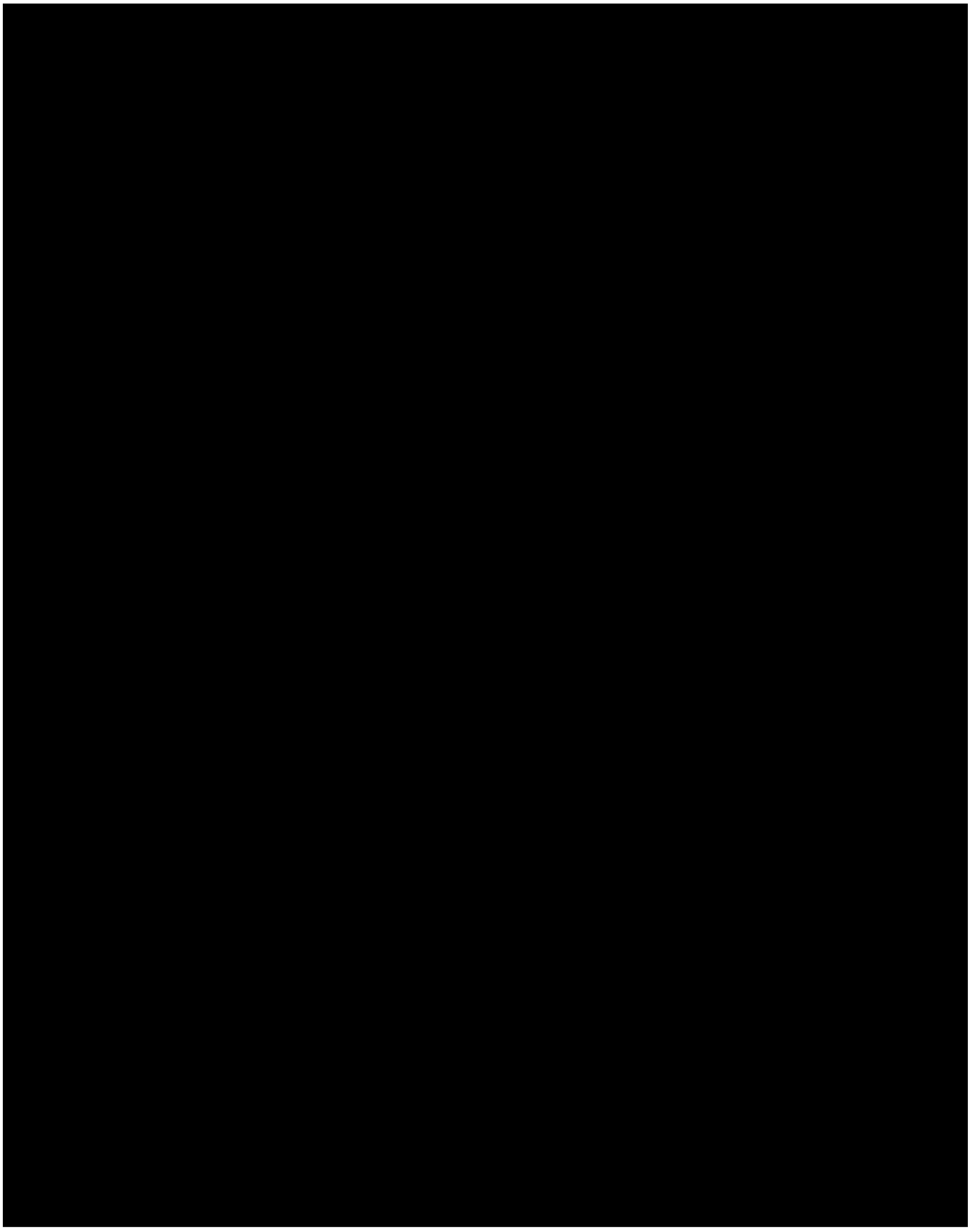
Improvements in T-VASI were observed for both Week 24 and Week 52. The proportion of participants who achieved a T-VASI50 at Week 24 was also statistically significantly greater for ruxolitinib cream 0.15% QD, 0.5% QD, 1.5% QD, and 1.5% BID compared with vehicle with response rates of 16.1%, 6.5%%, 23.3%,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

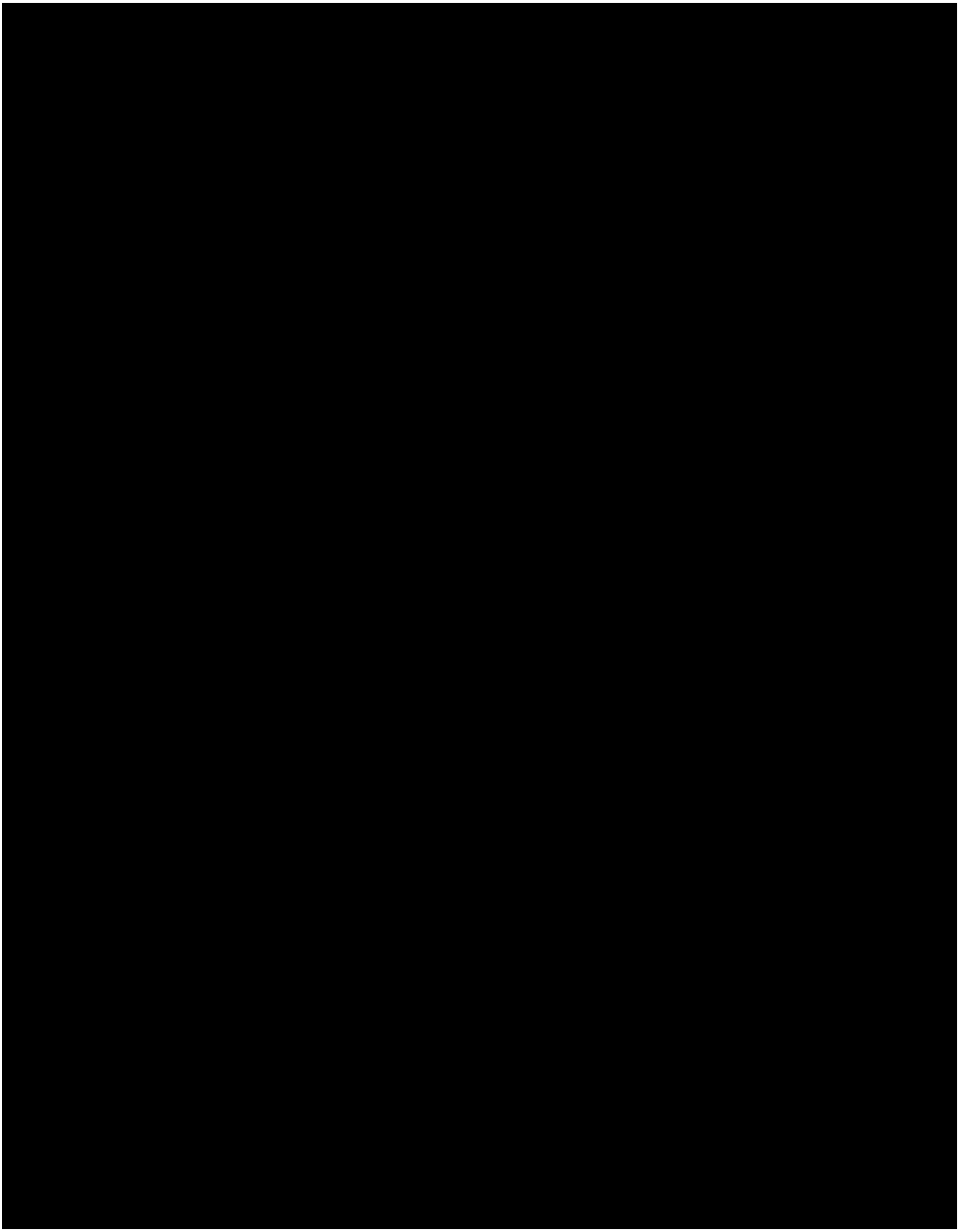
of 25.8%, 30.0%, and 36.4%, respectively. Similar to F-VASI, large effect sizes (Cohen's D = 1.24) is observed based on percentage change from baseline between ruxolitinib cream 1.5%BID and vehicle.

Compared with F-VASI, improvement in T-VASI was slower. This observation is not unexpected given that repigmentation on the body and acral areas progresses at a slower rate than facial repigmentation. Despite that, response rates for the F-VASI50, F-VASI75, and T-VASI50 favored the higher strength treatment regimens (both 1.5% QD and 1.5% BID) versus vehicle at Week 24 and 1.5% BID regimen at Week 52 across the endpoints. Given that many participants may not achieve peak response by Week 24 and that there are constraints to the length of the vehicle period, the 1.5% BID regimen appears to have given a higher response over time. Key secondary endpoints including percentage change in F-BSA, F-PhGVA, and PaGIC also followed a similar pattern, with separation from vehicle at Week 24 and continued improvement through Week 52.

All ruxolitinib treatment arms were generally safe and well-tolerated with no significant TEAEs or application site events and no clinically relevant hematological changes. TEAE rate overall is low and similar between active treatment and vehicle treatment. There were 4 SAEs through 52 weeks and all of them were not treatment-related. Discontinuations from treatment through 52 weeks was low. Safety and tolerability were similar between the Week 24 and Week 52 period. [redacted]







3. OBJECTIVES AND ENDPOINTS

Table 8 presents the objectives and endpoints.

Table 8: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of ruxolitinib cream in participants with vitiligo.	• Proportion of participants achieving F-VASI75 at Week 24.
Key Secondary	
To further assess the efficacy of ruxolitinib cream.	• Proportion of participants achieving F-VASI50 at Week 24. • Proportion of participants achieving F-VASI90 at Week 24. • Proportion of participants achieving T-VASI50 at Week 24. • Proportion of participants achieving a VNS of "4 – A lot less noticeable" or "5 – No longer noticeable" at Week 24. • Percentage change from baseline in F-BSA at Week 24.
Secondary	
To evaluate the safety and tolerability of ruxolitinib cream.	• The frequency, duration, and severity of AEs; physical examinations; vital signs; and laboratory data for hematology and serum chemistry.
To further assess the efficacy of ruxolitinib cream.	• Proportion of participants achieving F-VASI25/50/75/90 during the treatment period (double-blind and treatment extension periods). • Percentage change from baseline in F-VASI during the treatment period (double-blind and treatment extension periods). • Percentage change from baseline in F-BSA during the treatment period (double-blind and treatment extension periods). • Percentage change from baseline in T-VASI during the treatment period (double-blind and treatment extension periods). • Percentage change from baseline in T-BSA during the treatment period (double-blind and treatment extension periods). • Proportion of participants achieving T-VASI25/50/75/90 during the treatment period (double-blind and treatment extension periods). • Proportion of participants in each category of VNS during the treatment period (double-blind and treatment extension periods).

Table 8: Objectives and Endpoints (Continued)

Objectives	Endpoints
Secondary (continued)	
To evaluate the ruxolitinib PK in plasma after treatment of ruxolitinib cream.	• Population-based (trough) plasma concentrations of ruxolitinib at Weeks 4, 24 and 40.
Exploratory	
To further assess the efficacy of ruxolitinib cream.	• Proportion of participants achieving an F-PhGVA of clear (0) or almost clear (1) during the treatment period (double-blind and treatment extension periods). • Proportion of participants achieving an T-PhGVA of clear (0) or almost clear (1) during the treatment period (double-blind and treatment extension periods). • Proportion of participants in each F-PhGVA category during the treatment period (double-blind and treatment extension periods). • Proportion of participants in each T-PhGVA category during the treatment period (double-blind and treatment extension periods). • Proportion of participants who report F-PaGIC-V of very much improved or much improved during the treatment period (double-blind and treatment extension periods). • Proportion of participants in each F-PaGIC-V category during the treatment period (double-blind and treatment extension periods). • Proportion of participants who report T-PaGIC-V of very much improved or much improved during the treatment period (double-blind and treatment extension periods). • Proportion of participants in each T-PaGIC-V category during the treatment period (double-blind and treatment extension periods). • Proportion of participant in each category for the color-matching question during the treatment period (double-blind and treatment extension periods).

Table 8: Objectives and Endpoints (Continued)

Objectives	Endpoints
Exploratory (continued)	
To determine the participants' quality of life.	• Change from baseline in DLQI (or CDLQI) during the treatment period (double-blind and treatment extension periods). • Change from baseline in WHO-5 during the treatment period (double-blind and treatment extension periods). • Change from baseline in TSQM during the treatment period (double-blind and treatment extension periods). • Change from baseline in VitiQoL during the treatment period (double-blind and treatment extension periods). • Change from baseline in HADS during the treatment period (double-blind and treatment extension periods).
To evaluate translational biomarkers in the blood of participants treated with ruxolitinib cream.	• Change from baseline in the expression of select biomarkers in peripheral blood at Weeks 12, 24, 40, and 52.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, vehicle-controlled study 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, ≥ 3 T-VASI, and for whom total body involved vitiligo area (facial and nonfacial) does not exceed 10% BSA. Approximately 300 participants will be randomized 2:1 to receive initial study treatment (ruxolitinib cream 1.5% BID:vehicle) for 24 weeks (see Figure 1). Participants will be stratified by region (North America or Europe) and skin type (Fitzpatrick scale Type I and II vs Type III, IV, V, and VI). Adolescents (≥ 12 to < 18 years) will make up at least 10% of the study population, and no more than 50% of participants will be > 40 years old.

During the double-blind, vehicle-controlled period, participants will receive ruxolitinib cream 1.5% BID or vehicle for 24 weeks to be applied to depigmented areas only on the face and body up to 10% total BSA. Participants should continue to treat depigmented areas identified for treatment at baseline even if the area begins to improve or fully repigment.

After completion of the Week 24 assessments, participants will be offered the opportunity to continue in the treatment extension period. Participants initially randomized to vehicle will be crossed over to active drug, and participants treated with ruxolitinib cream will receive an additional 28 weeks of treatment with ruxolitinib cream 1.5% BID. To be eligible for the treatment extension, participants must have completed the baseline and Week 24 visit assessments, be compliant with study procedures, and not have any safety issues. During the treatment extension, participants should continue to treat depigmented areas identified for treatment at baseline even if the area begins to improve or fully repigment. Total treated areas (facial and nonfacial areas) should not exceed to 10% BSA.

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

Following the last application of ruxolitinib cream at Week 52, there will be a 30-day safety follow-up period to evaluate safety and duration of response.

Participants who successfully complete the 52-week treatment in this study may be eligible to participate in a separate extension study to evaluate durability of effect and maintenance regimens.

See Section 6.5 for detailed information of study drug modification and application guidance.

4.2. Overall Study Duration

Screening is up to 32 days (~4 weeks); the double-blind, vehicle-controlled treatment period is 24 weeks; the treatment extension period is 28 weeks; and safety follow-up is 30 days. Total duration is up to approximately 60 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 prohibited 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. 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 A.

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.

5.2. Exclusion Criteria

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

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 according to the CDC BMI Percentile Calculator for Child and Teen (2019).
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.

5.3. Lifestyle Considerations

Participants should be cautioned 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.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study treatment. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes that the participant would be eligible if retested. Additionally, a participant who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status or any laboratory abnormality is inconsistent with the participant's medical history. Participants who rescreen must be assigned a new screening number.

5.5. Replacement of Participants

Participants will not be replaced during the study.

6. STUDY TREATMENT

6.1. Study Treatment Application

Table 9 presents the study treatment information.

Table 9: 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:	Double-blind and treatment extension periods: BID. A thin film is applied to depigmented vitiligo areas.	Double-blind period: BID. A thin film is applied to the depigmented vitiligo areas. Treatment extension period: Not applicable.
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 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 study of 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.

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

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

- Participants should apply study drug only to depigmented vitiligo areas identified by the investigators 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 even if the area begins to improve or fully repigment.

6.1.2. Application During the Treatment Extension Period

During treatment extension period (Week 24 to Week 52), participants should follow the below study drug application guidance:

- Participants should apply study drug to depigmented vitiligo areas identified by the investigators up to a T-BSA (facial and nonfacial) of ≤ 10% BSA.
- Participants should continue to treat all depigmented vitiligo areas identified by the investigators for treatment at baseline even if the area begins to improve or fully repigment.
- Participants who have an expansion of existing areas of vitiligo during the course of the treatment extension period may treat these areas identified by the investigators 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.

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 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. The system will assign in a 2:1 ratio (ruxolitinib cream 1.5% BID:vehicle), stratified by region (North America or Europe) and skin type (Fitzpatrick scale Type I and II vs Type III, IV, V, and VI). Adolescents will make up at least 10% or participants, and no more than 50% of participants will be aged greater than 40 years. The IRT will assign participant ID numbers, track participant visits, randomize participants according to the defined parameters, maintain the blinding, and manage study drug inventory. Full details will be provided in the IRT Manual. Study treatment will be dispensed at the study visits summarized in the Schedule of Activities (see Table 3 and Table 4).

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

6.4. Study Treatment Compliance

Compliance with all study-related treatments must be emphasized to the participant by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with ruxolitinib cream 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 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 ruxolitinib cream. Except in cases of emergency, it is recommended that any findings of concern (eg, AE) be confirmed and that the investigator consult with the sponsor medical monitor (or other representative of the sponsor) before interrupting study drug. Additionally, the investigator must obtain approval from the sponsor before restarting study drug. Participants who experience a recurrence of the initial AEs upon restarting the study drug may need the study drug to be permanently discontinued.

Instructions for application interruptions for ruxolitinib cream are outlined in Table 10. Individual decisions regarding interruptions should be made using clinical judgment in consultation with the medical monitor (whenever possible), taking into account relatedness of the AE to the study treatment and the participant's underlying condition.

Table 10: 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 or higher 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 Due to an Adverse Event

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:

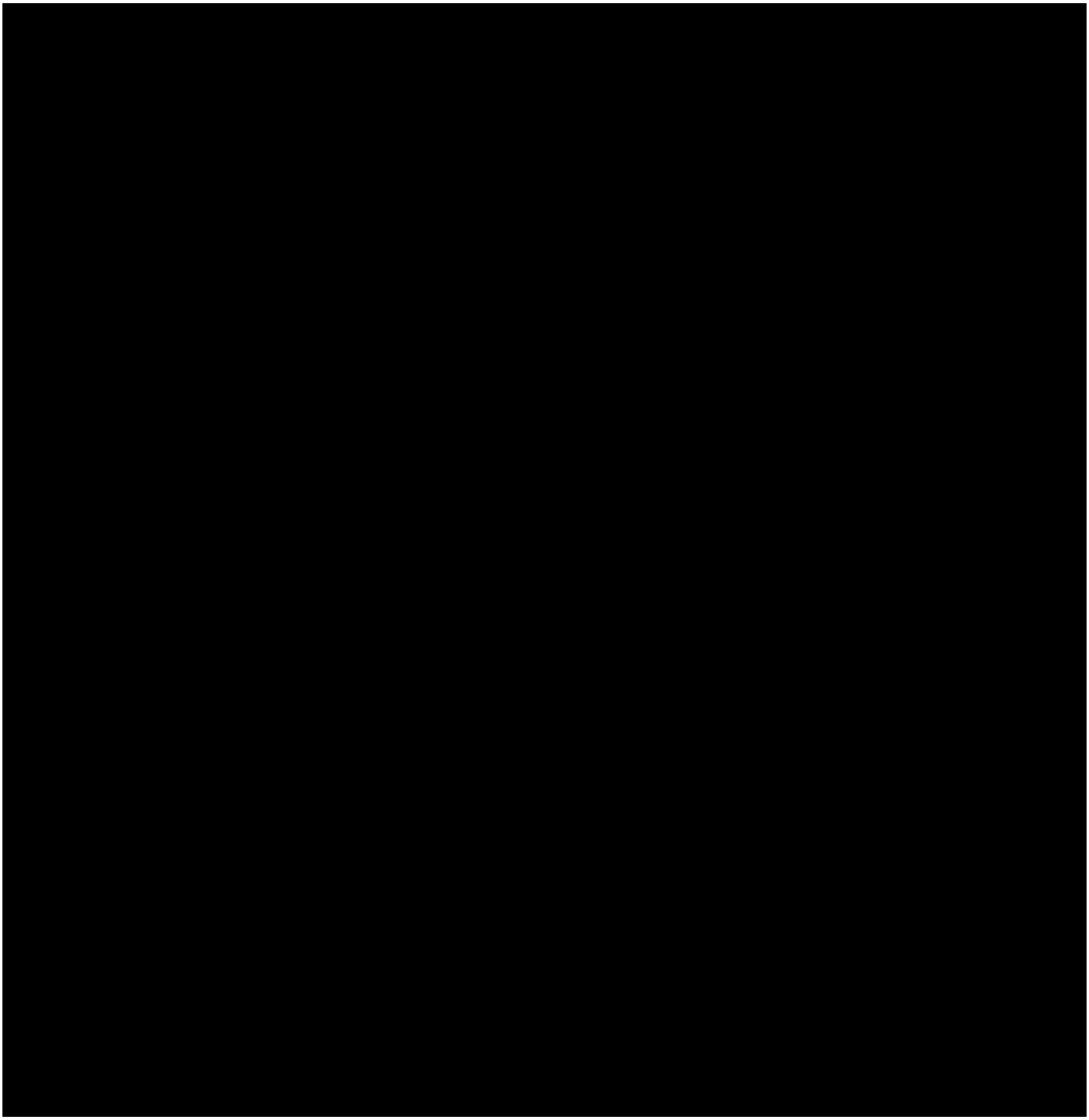
- Occurrence of an AE that is related to treatment with the study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the participant's ability to continue study-specific procedures or continuing treatment is considered to not be in the participant's best interest.
- 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 recorded in the eCRF. Any prior medication received up to 32 days before the first dose of study treatment 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 or prior therapy.



6.8. Treatment After the End of the Study

Participants who successfully complete the 52-week treatment in this study may be eligible to participate in a separate extension study to evaluate durability of effect and maintenance regimens.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

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

- A participant is found not to have met eligibility criteria (any exclusion criterion or any inclusion 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 (EOT1 or EOT2 depending on the period during with the participant discontinues treatment). Reasonable efforts should be made to have the participant return for a safety follow-up visit. The last date of the last dose of study drug(s)/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 drug/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 and Table 4 for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-Up

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

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

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

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.
- Participants who are rescreened are required to sign a new ICF.

8.1.2. Screening Procedures

Screening is the interval between signing the ICF and the day that the participant is assigned to the study drug (Day 1). Screening assessments for determination of eligibility may be performed over a period lasting up to 32 days.

Procedures conducted as part of the participant's routine clinical management (eg, clinical laboratory tests) and collected before informed consent is obtained may be used for screening or baseline purposes, provided the procedure meets the Protocol-defined criteria and has been performed within 32 days before Day 1. All information associated with eligibility requirements, including demography and medical history, must be entered into the appropriate eCRF pages.

Results from the screening assessments will be reviewed by the investigators to confirm eligibility before Day 1 and administration of study drug. Tests results that fail eligibility requirements may be repeated once during screening if the investigator believes that the participant would be eligible if retested. For screening assessments that are repeated, the most recent available result before administration of study drug will be used to determine eligibility. See Section 5.4 regarding screen failures.

Participants aged ≥ 12 to < 18 years screened in Germany and found to have hemoglobin between 10 g/dL and 12 g/dL should be assessed for the cause of the abnormality per local practice guidelines/institutional standard of care before randomization. This is a Germany-specific requirement. Specific cases may be reviewed with the medical monitor. Participants with hemoglobin < 10 g/dL are not enrolled per the exclusion criteria.

8.1.3. Interactive Response Technology Procedure

Each participant will be identified in the study by a participant ID number, which is a combination of the site ID and participant number. Site personnel should contact the IRT system to obtain the participant ID number during screening. Upon determining that the participant is eligible for study entry, the IRT system will be contacted to obtain the study 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 Study Reminder Cards and Diaries

Starting at the Day 1 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 Day 1 and at all visits (through Week 52). The reminder card will indicate the date/time of the next visit and will also remind the participant that they should have their application at the clinic during the visit under site supervision after their blood draws for PK and safety evaluations have been completed.

8.1.5. Demography and Medical History

8.1.5.1. Demographics and General Medical History

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

8.1.5.2. Disease Characteristics and Treatment History

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

8.2. Efficacy Assessments

8.2.1. Body Surface Area

Total % BSA (includes facial and nonfacial areas) depigmented by vitiligo will be estimated at each visit. Body surface area assessment will be performed by the Palmar Method. 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).

[redacted]

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

VASI = Σ [hand units] × [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.

8.2.3. Physician's Global Vitiligo Assessment (Facial)

The severity of vitiligo will be assessed by the physician using the PhGVA, which has a 5-point scale (Table 11). Response will be reported for face (F-PhGVA).

Table 11: Facial Physician's Global Vitiligo Assessment Scale

Score	Severity	Description
0	Clear	No signs of vitiligo or complete/near complete repigmentation
1	Almost Clear	Mostly pigmented areas with small depigmented or difficult to repigment areas (eg, philtrum, nares, corners of eyes, perioral skin)
2	Mild Disease	Modest areas of depigmentation (not more than half of facial skin) with approximately 50% pigmentation within vitiligo areas or significant perifollicular pattern present
3	Moderate Disease	Large areas of depigmented vitiligo areas (more than half of facial skin); significant depigmentation within vitiligo areas
4	Severe Disease	Extensive areas of vitiligo to complete depigmentation on face

8.2.4. Physician's Global Vitiligo Assessment (Total Body)

The severity of total body vitiligo will be assessed by the physician using the PhGVA, which has a 5-point scale (Table 12). Response will be reported for total body (T-PhGVA).

Table 12: Total Body Physician's Global Vitiligo Assessment Scale

Score	Severity	Description
0	Clear	No signs of vitiligo or complete/near complete repigmentation
1	Almost Clear	Mostly pigmented areas with small depigmented or difficult to repigment areas (eg, hands, feet, philtrum, nares, corners of eyes, perioral skin)
2	Mild Disease	Modest areas of depigmentation with approximately 50% pigmentation within vitiligo areas or significant perifollicular pattern present
3	Moderate Disease	Large areas of depigmented vitiligo areas; significant depigmentation within vitiligo areas
4	Severe Disease	Extensive areas of vitiligo with complete depigmentation

8.2.5. Photography

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

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

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

Patient-reported outcomes and quality of life will be assessed (see Table 3 and Table 4) using the following tools:

- VNS (Section 8.2.6.1)
- Color-matching question (Section 8.2.6.2)
- F-PaGIC-V (Section 8.2.6.3)
- T-PaGIC-V (Section 8.2.6.4)
- DLQI or CDLQI (Section 8.2.6.5)
- WHO-5 (Section 8.2.6.6)

- TSQM (Section 8.2.6.7)
- VitiQoL (Section 8.2.6.8)
- HADS (Section 8.2.6.9)

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 prior to discussions with the investigator or study site staff.

At the baseline visit, all patient-reported outcomes must be completed before the participant's first study drug application.

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 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.

8.2.6.2. Color-Matching Question

The baseline photograph and current participants' facial image (participants will be provided a mirror) will be shown to the participant for reference, and the participant will be asked to respond to the following query:

> At this point of your treatment, how well does your skin color match between your face treated vitiligo skin and face normal skin? Responses: (1) Excellent, (2) Very good, (3) Good, (4) Poor, and (5) Very poor.

8.2.6.3. Patient Global Impression of Change-Vitiligo (Facial)

The F-PaGIC-V is an assessment of improvement by the participant. It is a 7-point scale comparing the vitiligo areas at baseline with the participant's treated areas of facial vitiligo at the study visit. Response will be reported for face (F-PaGIC-V). The baseline photograph and current participants' facial image (participants will be provided a mirror) will be shown to the participant for reference. The participant will be asked to respond to the following query:

> Since the start of the treatment you've received in this study, your vitiligo on your face treated with the study drug is: (1) Very much improved, (2) Much improved, (3) Minimally improved, (4) No change, (5) Minimally worse, (6) Much worse, and (7) Very much worse.

F-PaGIC-V scores of 1 or 2 can be interpreted as representing treatment success.

8.2.6.4. Patient Global Impression of Change-Vitiligo (Total Body)

The T-PaGIC-V is an assessment of improvement by the participant. It is a 7-point scale comparing the vitiligo areas at baseline with the participant's treated areas of total body vitiligo at the study visit. Response will be reported for total body (T-PaGIC-V). The participant will be asked to respond to the following query:

> Since the start of the treatment you've received in this study, your vitiligo on your total body treated with the study drug is: (1) Very much improved, (2) Much improved, (3) Minimally improved, (4) No change, (5) Minimally worse, (6) Much worse, and (7) Very much worse.

T-PaGIC-V scores of 1 or 2 can be interpreted as representing treatment success.

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 ≥ 12 years to < 16 years at baseline, the CDLQI will be completed instead of the CDLQI throughout their participation in the 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.

8.2.6.6. WHO-5

The WHO-5 is a validated, self-administered, 5-item questionnaire designed to assess mental well-being over the past 2 weeks, which can be used as an outcome measure for the wanted and unwanted effects of treatments (WHO Collaborating Center for Mental Health, Topp et al 2015). The questionnaire consists of 5 statements, which respondents rate according to the following scale: 0 = At no time; 1 = Some of the time; 2 = Less than half of the time; 3 = More than half of the time; 4 = Most of the time; 5 = All of the time.

The raw score is calculated by totaling the figures of the 5 answers for a range of 0 to 25, with 0 representing the worst possible and 25 representing the best possible quality of life. A score below 13 indicates poor well-being.

Full details will be provided in the Study Manual.

8.2.6.7. Treatment Satisfaction Questionnaire for Medication

TSQM is a validated 9-item questionnaire that measures a participant's satisfaction with medication taken in a clinical study using a recall period of the past 2 to 3 weeks or since the medication was last used. The questionnaire uses a 7-point scale for each question (Bharmal et al 2009). Full details will be provided in the Study Manual.

8.2.6.8. VitiQoL

VitiQoL is a 15-item quality-of-life assessment that asks participants to rate various aspects of their condition during the past month using a 7-point scale ("Not at all" to "All of the time") (Lilly et al 2013). Full details will be provided in the Study Manual.

8.2.6.9. Hospital Anxiety and Depression Scale

HADS is 14-item questionnaire that assesses the levels of anxiety and depression that a person is currently experiencing (Zigmond and Snaith 1983). There are 7 questions each for measuring anxiety and for measuring depression, with 4 possible responses to each question (responses are scored as 0, 1, 2, or 3). Separate scores are calculated for anxiety and depression. Full details will be provided in the Study Manual.

8.3. Safety Assessments

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

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

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 30 days after the last dose of study 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. Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following-up on AEs that are serious, considered related to the study 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 during the screening process or between visits, or through physical examinations, laboratory tests, or other assessments. The definition, reporting, and recording requirements for AEs are described in Section 9.

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 and Table 4.

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

All 12-lead ECGs will be performed with the participant in a recumbent or semi-recumbent position after 5 minutes of rest. Electrocardiograms should be performed as indicated in Table 3. Additional 12-lead ECGs may be performed at other visits as deemed clinically necessary. Twelve-lead ECG performed within 2 months before baseline is acceptable for using as a screening value.

Electrocardiograms will be interpreted by the investigator at the site or designee, and the results will be used for immediate management of the participant's care. There is no central reader of ECGs for this study. The decision to include or exclude a participant or withdraw a participant from the study based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate. Any abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

8.3.5. Laboratory Assessments

Required laboratory tests are listed in Table 13, which include hematology, chemistry, urinalysis, serology, free T4, TSH, FSH, and pregnancy test (see Table 3 and Table 4). Clinical laboratory tests will be performed at a central laboratory (refer to the Laboratory Manual for sample handling and shipping instructions).

Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. All laboratory tests with values considered clinically significantly abnormal during participation in the study, or within 30 days after the last dose of study 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 13: Required Laboratory Analytes

<table>
<tr><th>Serum Chemistries[a]</th><th>Hematology</th><th>Urinalysis With Microscopic Examination</th><th>Serology</th><th>Other</th></tr>
<tr><td rowspan="3">Albumin
Alkaline phosphatase
ALT
AST
Bicarbonate or CO_2
Blood urea nitrogen or urea
Calcium
Chloride
Creatinine
Glucose
Lactate dehydrogenase
Phosphate
Potassium
Sodium
Total bilirubin
Direct bilirubin (if total bilirubin is elevated above ULN)
Total protein</td><td rowspan="3">Complete blood count, including:
• Hemoglobin
• Hematocrit
• Mean corpuscular volume (MCV)
• Platelet count
• Mean platelet volume
• Red blood cell count
• Reticulocyte count
• White blood cell count

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

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

8.3.5.1. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential during screening and at the safety follow-up visit (30 [+ 7] days after EOT; EOT1 or EOT2 as applicable). Urine pregnancy tests will be conducted as outlined in Table 3 and Table 4, as medically indicated, or per country-specific requirement. Urine pregnancy tests will be performed locally. If a urine pregnancy test is positive, the 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.

8.3.5.2. Serology

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

8.4. Pharmacokinetic Assessments

Venous blood samples will be collected to assess the PK of ruxolitinib cream in this study population 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 during study visits noted in the Table 3. 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.

8.5. Pharmacodynamic and Translational Assessments

Serum will be collected from all participants at all sites for proteomic analysis at timepoints outlined in Table 3 and Table 4. The purpose of this analysis will be to retrospectively evaluate correlative and pharmacodynamic biomarkers of response.

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

8.6. Unscheduled Visits

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

8.7. End of Treatment and/or Early Termination

If a decision is made that the participant will permanently discontinue study drug, then the EOT visit should be conducted (EOT1 or EOT2 depending on the study period when the participant discontinues). If the EOT visit coincides with a regular study visit, then the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT page in the eCRF. If this decision does not coincide with a regular visit, reasonable efforts should be made to have the participant return to the site to have the EOT procedures completed.

8.8. Safety Follow-Up

For participants who do not participate in a separate extension study, the safety follow-up period is the interval between the EOT visit (EOT1 or EOT2 depending on the study period when the participant discontinues) and the scheduled safety follow-up visit, which should occur 30 (+ 7) days after the EOT visit (or after the last dose of study drug/treatment 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/treatment, 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. If present before entering the study, the condition should be captured as medical history.
- 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. Conditions that were present at the time informed consent was given should be recorded on the Medical History 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 to sponsor or designee 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 the Adverse Event Form, and the treatment should be specified on the appropriate eCRF (eg, Prior/Concomitant Medications, Procedures and Non-Drug Therapy).

Assessment of Intensity

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

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

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2:** Moderate; minimal, local, or noninvasive intervention 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 intervention 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 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 IB and/or Product Information, for marketed products, 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 SAE follow-up 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 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 during the double-blind, vehicle-controlled period, if the investigator deems it necessary to determine optimal medical management of the participant, emergency unblinding will be performed exclusively by the Principal Investigator and subinvestigator as described in the IRT Study Manual. The IRT system has an option to select for "Emergency Code Break" action for a given participant. After entering the 6-digit study drug tube number and verification of the unmasking information, the investigator/subinvestigator will proceed to either final confirmation or cancellation of the code break procedure.

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

If an investigator, site personnel performing assessments, or participant is unblinded, the participant must 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 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

Approximately 300 participants will be randomized 2:1 to ruxolitinib cream 1.5% BID or vehicle and stratified by baseline skin type (Fitzpatrick scale Type I and II vs Type III, IV, V, and VI) and region (North America or Europe). The sample size is calculated to provide sufficient power (> 85%) to detect a difference between the 1.5% BID with the vehicle in primary and key secondary endpoints. The powers for different endpoints are provided in Table 14. The Fisher's exact test with a 2-sided alpha of 0.05 is used to provide a conservative evaluation of statistical power, and it is accurate when there is a small expected number of responders in the vehicle group.

Table 14: Powering for Primary and Key Secondary Endpoints

Endpoints	Response Rates in Ruxolitinib 1.5% BID[a]	Response Rates in Vehicle[a]	Power[b]
F-VASI75 at Week 24	20%	5%	95%
F-VASI50 at Week 24	30%	10%	95%
F-VASI90 at Week 24	10%	1%	88%
T-VASI50 at Week 24	10%	1%	88%
Vitiligo - VNS Response at Week 24	10%	1%	88%

[a] Based on the results from a Phase 2, randomized, dose-ranging study (INCB18424-211).
[b] Based on the Fisher's exact test with a 2-sided alpha of 0.05.

10.2. Populations for Analysis

The populations for analysis are presented in Table 15.

Table 15: Populations for Analysis

Population	Description
ITT	The ITT population includes all randomized participants. Treatment groups for this population will be defined according to the treatment assignment at randomization.
PP	The PP population includes randomized participants who are considered to be sufficiently compliant with the Protocol.
Safety	The safety population includes all participants who applied at least 1 dose of study drug. Treatment groups for this population will be determined according to the actual treatment the participant received on Day 1.
PK/ pharmacodynamic evaluable	The PK/pharmacodynamic evaluable population includes participants who applied at least 1 dose of ruxolitinib cream and provided at least 1 postdose blood sample for PK. The study pharmacokineticist will review data listings of participant administration and sample records to identify participants to be excluded from the analysis.

10.3. Statistical Analyses

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

The gatekeeping testing strategy for the primary and key secondary analyses will be implemented to control the overall Type I error rate, 2-sided $\alpha = 0.05$. These endpoints will be tested in a fixed sequence at 2-sided $\alpha = 0.05$ level in the following order:

- Proportion of participants achieving F-VASI75 at Week 24
- Proportion of participants achieving F-VASI50 at Week 24
- Proportion of participants achieving F-VASI90 at Week 24
- Proportion of participants achieving T-VASI50 at Week 24
- Vitiligo - VNS Response at Week 24
- Percentage change from baseline in F-BSA at Week 24

10.3.1. Efficacy Analyses

10.3.1.1. Primary Analysis

The primary analysis will be based on the intent-to-treat population. The primary alternative hypothesis (superiority of ruxolitinib cream 1.5% BID compared with vehicle) will be tested using exact logistic regression (Mehta and Patel 1995). This model will include the treatment group (1.5% BID and vehicle) and stratification factors. The p-value for between-treatment

group testing will be compared with 0.05. Odds ratio and corresponding 95% confidence interval will be provided for comparing ruxolitinib cream and vehicle group at Week 24.

All nonresponders in the double-blind treatment period, as well as all participants who discontinue study treatment at any time before the timepoint of interest, or discontinue from the study for any reason, will be defined as nonresponders for the nonresponder imputation analysis.

Analysis will also be performed in the PP population for the primary endpoint. The following deviations are considered major:

- Missing primary endpoints on F-VASI;
- Compliance less than 60% based on the application numbers.

Participants with 1 or more such deviations will be excluded from the PP population. In addition, Protocol deviations related to inclusion/exclusion criteria, discontinuation criteria, and use of excluded concomitant medications will be evaluated and decided whether they should be excluded. Any exclusion from the PP population will be decided prior to breaking the blind.

In addition, sensitivity analyses, including MI and LOCF, may be performed. For MI, a fully conditional specification method (van Buuren et al 2007) that assumes the existence of a joint distribution for all variables will be used to impute F-VASI scores. A regression model including treatment group, stratification factors, and baseline and postbaseline F-VASI scores up to Week 24 will be specified for the fully conditional specification method. After the missing values are imputed, the binary variables will be derived based on the definition. The randomization seed will set to be 18424307 and the imputation will be repeated 10 times to generate corresponding complete data sets, in order to reflect the uncertainty around the true value. Exact logistic regression will be applied to each imputed dataset, and then the results will be combined for the inference. For LOCF, for the participants who discontinue study treatment at any time before the timepoint of interest or discontinue from the study for any reason, the last observed nonmissing value will be used to fill in missing values at the timepoint of interest. A tipping point analysis will be conducted to examine the potential effects of missing data. The missing binary response on F-VASI75 at Week 24 in each treatment group will be replaced by a range of values from the most conservative case to the most aggressive case. The most conservative case is that all the missing participants in active treatment groups are nonresponders and all the missing participants in the placebo group are responders, while the most aggressive case is the other way around. For each scenario, between-treatment comparisons will be performed using a chi-square test.

Subgroup analysis by baseline character, for example, skin type, age, and region, will be performed. Details will be provided in the Statistical Analysis Plan.

10.3.1.2. Key Secondary Analysis

If the primary objective is achieved, the statistical hypotheses for key secondary endpoints will be tested in the frequency specified in Section 10.3.

Key secondary efficacy analyses at Week 24 will be conducted in the ITT population. The statistical comparisons for binary outcomes (VASI50/90 and VNS response) will be analyzed using the similar method as specified in the primary analysis. For F-BSA, the missing values at Week 24 will be imputed using the similar multiple imputation method specified in the primary

analysis. Then the derived percentage change from baseline in F-BSA at Week 24 will be analyzed using an ANCOVA model with treatment group, stratification factors, and baseline value as covariates. A test for superiority between INCB018424 1.5% BID and vehicle cream will be performed using the least squares mean estimate of the percentage change from baseline in F-BSA at Week 24 from the ANCOVA model specified above. Superiority will be established if the p-value of the difference (INCB018424 1.5% BID minus vehicle) is less than 0.05.

10.3.1.3. Secondary Analysis

All other secondary and exploratory efficacy variables will be summarized using descriptive statistics. For categorical measurements, summary statistics will include sample size, frequency, and percentages. Similar exact logistic regression models as specified in the primary and key secondary analysis will be used if applicable. For continuous measurements, summary statistics will include sample size, mean, median, SD, standard error of the mean, minimum, and maximum. Continuous efficacy endpoints, including the actual measurement, change from baseline, and percentage change from baseline may also be analyzed by the mixed effect model with repeated measurement.

Secondary endpoint analyses at Week 52 on VASI (eg, F-VASI25/50/75/90 and T-VASI25/50/75/90) will be performed in the ITT population with the following methods:

- Participants who discontinue the study drug before Week 24 due to any reason will be defined as nonresponders for subsequent visits until Week 52.
- For participants who completed Week 24 in the vehicle and 1.5% BID group, missing values of VASI in treatment extension period (including Week 52) will be imputed using linear extrapolation method. The binary outcomes on responses, VASI50/75/90, will be derived based on the imputed values. The statistical comparisons for these endpoints will be analyzed using the similar method as specified in the primary analysis.

10.3.2. Safety Analyses

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 tabulated by the MedDRA preferred term and system organ class. Severity of AEs will be based on the National Cancer Institute 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.

The clinical laboratory data will be analyzed using summary statistics; no formal treatment group comparisons are planned. 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 and shift tables relative to baseline will be tabulated.

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. Analysis Plan

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

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

- The Protocol, Protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements, the policies and procedures established by the IRB/IEC, and institutional requirements.
- Any amendments to the Protocol will require 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. 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 designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

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[ab]
- Sexual abstinence[c]

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

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

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

[b] Vasectomized partner is a highly effective method of avoiding pregnancy provided that 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 Trials Facilitation and Coordination Group 2014.

APPENDIX B. WHO CLASSIFICATION OF TOPICAL CORTICOSTEROIDS

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

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

Source: WHO 1997.

APPENDIX C. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1:	31 OCT 2019
Amendment 2:	12 DEC 2019
Amendment 3:	21 FEB 2020
Amendment 3-US-CA:	13 MAR 2020

Amendment 3-US-CA (13 MAR 2020)

Overall Rationale for the Amendment: To clarify BMI criteria for adult and adolescent participants.

1. **Section 5.2, Exclusion Criteria**

   Description of changes: Added BMI-for-age criterion for adolescent participants (≥ 12 to < 18 years) to exclusion criterion 8.

   Rationale for change: Body mass index is interpreted differently for children and teens, even though it is calculated using the same formula as adult BMI. For children and teens, BMI needs to be age- and sex-specific. The normal or healthy weight category for BMI in children and teens per CDC is ≥ 5th to < 85th percentile range. Therefore, for adolescent participants the BMI-for-age ≥ 5th to < 85th percentile ranking is considered eligible for this study.

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

Amendment 3 (21 FEB 2020)

Overall Rationale for the Amendment: The primary purpose of this amendment is to incorporate revisions requested by the German and French Ethics Committees (ECs) and FDA.

1. **Section 1, Protocol Summary (Table 1: Primary and Secondary Objectives and Endpoints); Section 3, Objectives and Endpoints (Table 8: :Objectives and Endpoints); Section 10.1, Sample Size Determination (Table 14: Powering for Primary and Key Secondary Endpoints); Section 10.3, Statistical Analyses, Section 10.3.1.1, Primary Analysis; Section 10.3.1.2, Key Secondary Analysis; Section 10.3.1.3, Secondary Analysis**

   Description of changes: Reordered and revised the key secondary endpoints and updated the analysis plan.

   Rationale for change: To address FDA response.

2. **Section 1, Protocol Summary (Table 2: Key Study Design Elements)**

   Description of changes: Added 1 key exclusion criteria (exclude other forms of vitiligo) to the Population section, added information about the exit interview in the Study Design section, and added a DSMB section to indicate that a DSMB is not required in this study.

   Rationale for change: To address French EC response.

3. **Section 1, Protocol Summary (Table 3: Schedule of Activities: Double-Blind, Vehicle-Controlled Treatment Period [Day 1-Week 24]; Table 4: Schedule of Activities: Treatment Extension Period [Week 28-Week 52])**

   Description of changes: Added language that per protocol Section 8.3.2, 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.

   Rationale for change: To clarify that targeted physical examination is not required unless there are symptoms reported by the participant, AEs, or other findings.

4. **Section 8.1.2, Screening Procedures**

   Description of changes: Added language to instruct that adolescent participants screened in Germany whose hemoglobin is between 10 g/dL and 12 g/dL during the screening visit should be further evaluated per local guidelines before being enrolled into the study.

   Rationale for change: To address German EC response.

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

Amendment 2 (12 DEC 2019)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to incorporate revisions requested by the Voluntary Harmonisation Procedure (VHP).

1. **Section 5.2, Exclusion Criteria**

   Description of change: Added language to exclude participant who has current and/or history of tuberculosis.

   Rationale for change: To address VHP response.

2. **Section 5.2, Exclusion Criteria**

   Description of changes: Added language to exclude participants who live with anyone participating in any current Incyte-sponsored ruxolitinib cream study.

   Rationale for change: To avoid study drug sharing and reinforce treatment compliance.

3. **Section 8.1.2, Screening Procedures**

   Description of changes: Added language to instruct that German participants whose hemoglobin is between 10 g/dL and 10.5 g/dL during the screening visit should be further evaluated per local guidelines before enrolling into the study.

   Rationale for change: To address VHP response.

Amendment 1 (31 OCT 2019)

Overall Rationale for the Amendment:

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, because it does not have a significant impact on the safety or physical/mental integrity of the participants nor on the scientific value of the study.

The primary purpose of this amendment is to incorporate revisions requested by the Voluntary Harmonisation Procedure (VHP) and to add the option for a subgroup of study participants to be included in a substudy involving exit interviews at Week 24 and Week 52.

1. **Section 1, Protocol Summary (Table 3: Schedule of Activities: Double-Blind, Vehicle-Controlled Treatment Period [Day 1-Week 24]; Table 4: Schedule of Activities: Treatment Extension Period [Week 28-Week 52]); Section 8.1.6, Exit Interviews**

   Description of change: Exit interviews and informed consent to participate in them were added to the Schedule of Activities, and a description of the exit interview was added.

   Rationale for change: To provide details on the exit interviews and their timing, duration, and numbers of participants involved in the substudy.

2. **Section 2.5.1, Scientific Rationale for Study Design**

   Description of changes: Added the meaning and medical/clinical relevance of endpoints and their outcomes.

   Rationale for change: To address VHP response.

3. **Section 2.4, Ruxolitinib Cream**

   Description of changes: Added language “no precautions are anticipated for [ruxolitinib cream’s] concomitant use with systemic drugs or for participants with hepatic impairment.”

   Rationale for change: To address VHP response and add a statement regarding participants with hepatic function impairment.

4. **Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

   Description of change: The following footnote was removed: Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.

   Rationale for change: The statement is specific for oral ruxolitinib, as most of hormonal contraception is metabolized by the same enzyme (CYP3A4) for ruxolitinib. The systemic exposure for topical application of ruxolitinib cream is expected to be very limited. Thus, this precaution is not warranted.

5. **Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

   Description of change: Added footnote and clarified that the acceptable birth control methods that result in a failure rate of more than 1% per year are for US and Canada participants only.

   Rationale: To address VHP response.

6. **Section 1, Protocol Summary (Table 3: Schedule of Activities: Double-Blind, Vehicle-Controlled Treatment Period [Day1-Week 24]); Section 5.1, Inclusion Criteria**

   Description of change: Updated the definition of postmenopausal state to having amenorrhea for at least 12 months without an alternative medical cause.

   Rationale for change: To address VHP request and provide completed definition of postmenopausal.

7. **Section 5.2, Exclusion Criteria (Exclusion Criterion 12)**

   Description of change: Added language in exclusion criteria to exclude participants with known allergy or reaction to any component of the study formulation.

   Rationale for change: To address VHP request.

8. **Section 5.3, Lifestyle Considerations; Section 6.6.1, Permitted Medications and Procedures**

   Description of changes: Updated the study drug application guidance with respect to emollients, camouflage makeups, sunscreens, and after shaving.

   Rationale for change: To remove unnecessary limitation of concomitant application of study drug and other cosmetic products.

9. **Section 6.2, Preparation, Handling, and Accountability**

   Description of changes: Added language of application guidance for participants with hand vitiligo.

   Rationale for change: If patients have vitiligo on their hands, they do not need to wash the hand after study drug application.

10. **Section 6.6.2, Restricted Medications and Measures; Appendix B, WHO Classification of Topical Corticosteroids**

    Description of changes: Added WHO classification of topical corticosteroids.

    Rationale for change: To address VHP response and provide topical corticosteroid classification that combines system for both the United States and most of the European VHP countries.

11. **Section 8.2.6.3, Patient Global Impression of Change-Vitiligo (Facial)**

    Description of changes: Added that the baseline photograph and a mirror will be provided to the participant for reference.

    Rationale for change: To allow participants to self-evaluate the before and after treatment facial repigmentation while they answer the F-PaGIC.

12. **Section 1, Protocol Summary (Table 4: Schedule of Activities: Treatment Extension Period (Week 28-Week 52)])**

    Description of changes: Added "Assess compliance" up to Week 52 visits.

    Rationale for change: To further evaluate the compliance in the treatment extension period.

13. **Section 7.1.1, Reasons for Discontinuation**

    Description of changes: Language for participants found not to have met eligibility criteria was updated from "may be discontinued from study treatment" to "must be discontinued from study treatment." Also added definition of "not met eligibility criteria."

    Rationale for change: To address VHP response.

14. **Section 8.3.1, Adverse Events; Section 9.3, Recording and Follow-Up of Adverse Events and/or Serious Adverse Events; Section 9.4, Reporting of Serious Adverse Events**

    Description of changes: Updated SAE reporting timeframe from "within 24 hours" to "immediately, without undue delay, under no circumstances later than 24 hours following knowledge of the event."

    Rationale for change: To address VHP response.

15. **Section 9.3, Recording and Follow-Up of Adverse Events and/or Serious Adverse Events**

    Description of changes: Revised the language on "Assessment of Causality."

    Rationale for change: To address VHP response.

16. **Section 11.5, Publication Policy**

    Description of changes: Added language of "Sponsor commits to also adhere to supranational/international rules regarding publishing research results, as set by the Helsinki Declaration."

    Rationale for change: To address VHP response.

17. **Section 1, Protocol Summary; Section 4.1, Overall Design; Section 6.3, Measures to Minimize Bias: Randomization and Blinding; Section 10.1, Sample Size Determination**

    Description of changes: Removed the stratification criterion by age and added in stratification by region (North America or Europe).

    Rationale for change: To address VHP response and include region as one of stratification factors.

18. **Section 10.3.1.1, Primary Analysis**

    Description of changes: Revised the definition of per protocol (PP) population and clarified the language of primary analysis.

    Rationale for change: To address VHP response.

19. **Section 2.4.2.2.3, Vitiligo**

    Description of changes: Added language to address the observed effect size/efficacy rate of ruxolitinib cream (Cohen's D), and the expected effect size/efficacy rate of 1.5% BID.

    Rationale for change: To address VHP request.

20. **Section 5.1, Inclusion Criteria (Inclusion Criterion 5)**

    Description of change: Revised language in the inclusion criterion to clarify that for adolescent participants, the written informed consent of the parents or legal guardian and written assent from the adolescent participant are required. Adult participants must possess the ability to comprehend and willingness to sign an ICF.

    Rationale for change: To address VHP request.

21. **Section 10.3.1.1, Primary Analysis; Section 10.3.1.3, Secondary Analysis**

    Description of changes: The exact logistic regression will be used for primary and key secondary analysis.

    Rationale of change: To address VHP response.

22. **Section 3, Objectives and Endpoints (Table 8: Objectives and Endpoints); Section 8.2.6, Patient-Reported Outcomes**

    Description of changes: Moved F-PhGVA, T-PhGVA, F-PaGIC-V, T-PaGIC-V, and color-matching endpoints from quality-of-life objective to efficacy objective.

    Rationale for change: These are efficacy assessments not intended to evaluate patient quality of life.

23. **Section 1, Protocol Summary (Table 3: Schedule of Activities: Double-Blind, Vehicle-Controlled Treatment Period [Day1-Week 24]; Table 4: Schedule of Activities: Treatment Extension Period [Week 28-Week 52])**

    Description of changes: Removed re-dispended study drug language.

    Rationale for changes: Unused study drugs and tubes will not be re-dispensed in this study.

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