Official Title: An Open-Label, Phase 2, Safety, and Efficacy Study of Ruxolitinib Cream in Participants With Genital Vitiligo

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Clinical Study Protocol

INCB 18424-219

An Open-Label, Phase 2, Safety, and Efficacy Study of Ruxolitinib Cream in Participants With Genital Vitiligo

Product:	**INCB018424 (ruxolitinib cream)**
IND Number:	[redacted]
EU CT Number:	**2023-503737-22-00**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803 USA**
Original Protocol:	**06 OCT 2022**
Amendment 1:	**28 FEB 2023**

INVESTIGATOR'S AGREEMENT

I have read the INCB 18424-219 Protocol Amendment 1 (dated 28 FEB 2023) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

(Printed Name of Investigator)

(Signature of Investigator) (Date)

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[redacted]

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LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice daily
BSA	body surface area
CFR	Code of Federal Regulations
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
EOT	end of treatment
ET	early termination
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
F-VASI50/75/90	≥ 50%/75%/90% improvement in facial Vitiligo Area Scoring Index
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HIPAA	Health Insurance Portability and Accountability Act of 1996
HPV	human papilloma virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC_{50}	concentration that results in 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	identification
IEC	independent ethics committee
IRB	institutional review board
IRT	interactive response technology

Abbreviations and Special Terms	Definition
ISO	International Organization for Standardization
JAK	Janus kinase
MedDRA	Medical Dictionary for Regulatory Activities
NRS	numeric rating scale
[redacted]	[redacted]
[redacted]	[redacted]
PK	pharmacokinetic(s)
PRO	patient-reported outcome
[redacted]	[redacted]
RSI	Reference Safety Information
SAE	serious adverse event
SoA	schedule of activities
SOP	standard operating procedure
SPF	sun protection factor
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
TYK	tyrosine kinase
ULN	upper limit of normal
US	United States
UV	ultraviolet
VASI	Vitiligo Area Scoring Index
[redacted]	[redacted]
[redacted]	[redacted]
WOCBP	woman of childbearing potential

1. PROTOCOL SUMMARY

Protocol Title: An Open-Label, Phase 2, Safety, and Efficacy Study of Ruxolitinib Cream in Participants With Genital Vitiligo

Protocol Number: INCB 18424-219

Objectives and Endpoints:

Table 1 presents the primary objective and endpoint.

Table 1: Primary Objective and Endpoint

Objective	Endpoint
Primary	
To evaluate the efficacy of ruxolitinib cream in participants with genital vitiligo.	Proportion of participants achieving a genital VNS of "4 – A lot less noticeable" or "5 – No longer noticeable" at Week 48.

Overall Design:

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

Table 2: Key Study Design Elements

Study Phase	Phase 2
Clinical Indication	Nonsegmental vitiligo with genital involvement
Population	Males and females, aged ≥ 18 years, who have nonsegmental vitiligo with ≥ 0.25% BSA of vitiligo in the genital area (with a ≥ 0.1% BSA target lesion), vitiligo on other areas of the body, and total body vitiligo area not exceeding 10% BSA.
Number of Participants	Approximately 45 participants
Study Design	Open-label
Estimated Duration of Study Participation	Screening: Up to 30 days Treatment period: 48 weeks Safety follow-up: 30 days after last application of study drug Total: Up to approximately 56 weeks
Data Monitoring Committee	No
Coordinating Principal Investigator	To be determined

Treatment Groups and Duration:

This is an open-label study in which participants with nonsegmental vitiligo with genital involvement will receive ruxolitinib 1.5% cream BID for up to 48 weeks (see Figure 1). A minimum of 10 male and 10 female participants will be included. In addition, a minimum of 15 participants must have Fitzpatrick skin types 4 to 6, with at least 10 participants having Fitzpatrick skin type 5 or 6. Table 3 presents the SoA. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Figure 1: Study Design Schema

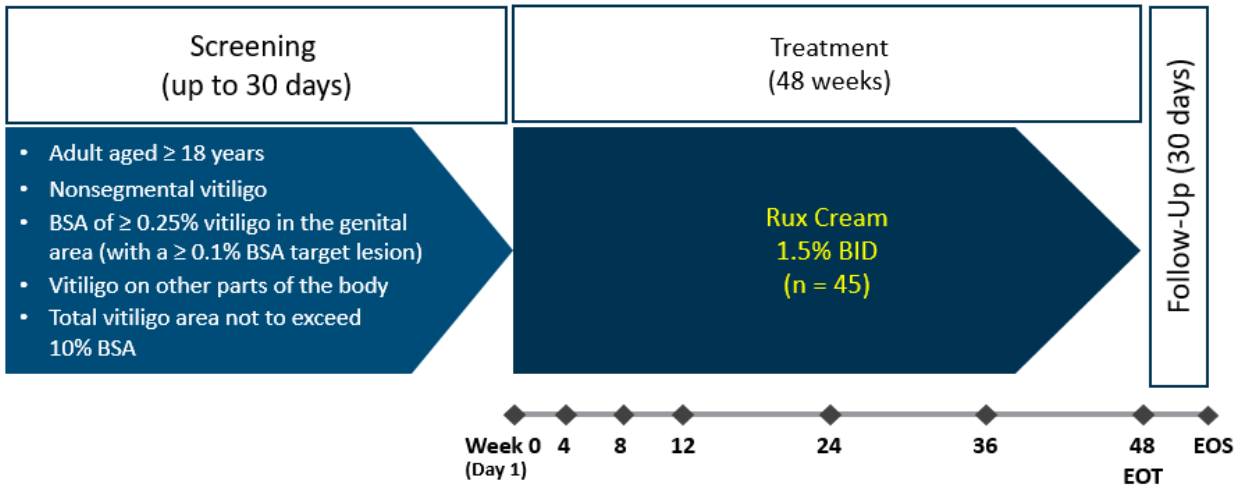


Table 3: Schedule of Activities

Procedure	Screening	Treatment[a]				Safety Follow-Up	Notes
	Days −30 to −1	Day 1	Week 4 (± 3 d)	Weeks 12, 24, 36 (± 7 d)	Week 48/ET (± 7 d) (EOT)	EOT + 30 Days (+ 7 d) (EOS)	
Administrative procedures							
Informed consent	X						
Contact IRT	X	X	X	X	X		
Inclusion and exclusion criteria	X	X					
Demography	X						
General and vitiligo medical history	X						
Prior/concomitant medications	X	X	X	X	X	X	
Apply study cream at site		X	X	X			On visit days, the participant should apply study cream to areas other than the genitals under direct supervision of the site staff; application to genital areas must also occur at the site, but not under supervision.
Dispense (D) and return (R) study cream and reminder/diary cards		D	R/D	R/D	R		All tubes of study cream to be weighed before dispensing and when returned.
Assess compliance of study cream			X	X	X		Compliance is based on the number of applications.
Safety assessments							
AE assessment	X	X	X	X	X	X	If an AE is noted, a targeted physical exam should be performed on relevant body systems. Ad hoc photography of skin-related AEs should occur as applicable.
Comprehensive physical examination	X				X		
Vital signs	X	X	X	X	X	X	
12-lead ECG	X						12-lead ECG performed within 2 months before Day 1 is acceptable.
Efficacy assessments							
Genital target lesion size	X	X	X	X	X	X	
BSA	X	X	X	X	X	X	Separate values will be collected for the 6 body regions, the genital region, and the face.
Percentage depigmentation	X	X	X	X	X	X	
[redacted]							
Photography of genital area	X	X*		X†	X		*If photo quality at screening is not adequate, the photography may be repeated on Day 1. †Week 24 only.

Table 3: Schedule of Activities (Continued)

Procedure	Screening	Treatment[a]				Safety Follow-Up	Notes
	Days −30 to −1	Day 1	Week 4 (± 3 d)	Weeks 12, 24, 36 (± 7 d)	Week 48/ET (± 7 d) (EOT)	EOT + 30 Days (+ 7 d) (EOS)	
PROs							Should be evaluated prior to any other study procedures/assessments.
Itch NRS	X	X	X	X	X		
[redacted]							The participant will be provided their baseline photo and a mirror to perform these assessments.
Color-matching question				X	X		
[redacted]							
Laboratory assessments							
Hematology and chemistry assessments	X	X		X*	X		*Week 24 only.
Thyroid testing	X						
Urinalysis	X						
FSH	X						Postmenopausal female participants only
Pregnancy testing (serum)	X					X	WOCBP only.
Pregnancy testing (urine)		X	X	X	X		WOCBP only.
[redacted]							

Note: Unscheduled visits may occur at any time at the investigator's discretion, and appropriate clinical and laboratory tests may be performed, as clinically indicated.
[a] Week 4 = Day 29, Week 8 = Day 57, Week 12 = Day 85, Week 24 = Day 169, Week 36 = Day 253, Week 48 = Day 337.

2. INTRODUCTION

2.1. Ruxolitinib Cream

Ruxolitinib cream (Opzelura™) is approved in the US for the topical treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older. Ruxolitinib cream is a topical formulation of ruxolitinib phosphate, an inhibitor of the JAK family of protein TYKs. Janus kinases are intracellular signaling enzymes that act downstream of key proinflammatory cytokines implicated in vitiligo pathogenesis. Ruxolitinib is a novel, potent, and selective inhibitor of the JAKs, specifically JAK1 and JAK2 with modest to marked selectivity against TYK2 and JAK3. Ruxolitinib potently (IC_{50} < 5 nM) inhibits JAKs, yet it does not significantly inhibit (< 30% inhibition) a broad panel of 28 kinases when tested at 200 nM (approximately 100 times the average IC_{50} value for JAK enzyme inhibition).

2.2. Disease Background

Vitiligo is an autoimmune pigmentary disease that is estimated to affect 0.5% to 2% of the population worldwide and is characterized by depigmented patches of skin with a selective loss of melanocytes (Krüger and Schallreuter 2012). 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). There are limited data on the incidence of genital vitiligo. Of patients with vitiligo, approximately one-third were reported to have genital involvement (Ezzedine et al 2019, Speeckaert and van Geel 2014). Therefore, based on 0.5% to 2% of the population having vitiligo, genital vitiligo is expected to be observed in 0.15% to 0.66% of the population (Dauendorffer et al 2022).

Vitiligo is considered a serious disease owing to its substantial psychological burden on patients and its progressive course if left untreated. Involvement of specific areas (eg, face, hands, genitals) can have a major negative impact on self-esteem and quality of life (Ezzedine et al 2019, Silverberg and Silverberg 2013). A meta-analysis of vitiligo and depression showed approximately 25% of patients with vitiligo had depression based on diagnostic codes and approximately 33% had depressive symptoms based on self-reports (Lai et al 2017). A study of vitiligo's impact showed that genital vitiligo is associated with significant impact on quality of life as assessed by the Dermatology Life Quality Index, with a significant correlation of the existence of genital lesions on sexual dysfunction (Silverberg and Silverberg 2013). Patients have noted that their genital vitiligo was feared and mistaken for a sexually transmitted disease or cancer (Talsania et al 2010).

Genital vitiligo is a difficult-to-treat location with poor response to treatment (Dauendorffer et al 2022). Ruxolitinib cream is the only treatment approved for repigmentation in patients with nonsegmental vitiligo. Prior to its approval in JUL 2022, the management of vitiligo was empirical and based on the most recent consensus guidelines (American Academy of Dermatology 2022, Gawkrodger et al 2008, Taieb et al 2013, Vitiligo Research Foundation 2022). The consensus guidelines note first-line treatment of vitiligo as topical steroids and calcineurin inhibitors. However, topical steroids cannot be used to treat sensitive areas, including the genital area, because of side effects such as skin atrophy. Topical calcineurin

inhibitors do not present this risk, but do have a risk of HPV reactivation (Dauendorffer et al 2022). Second-line treatments for vitiligo consist of phototherapy (narrow-band UVB and psoralen UVA) and systemic steroid treatment. However, phototherapy typically has disappointing results for genital vitiligo (Welsh et al 2009) and was found to be associated with an increased risk of genital squamous cell carcinoma (Mohammad et al 2017). Third-line treatments consist of surgical grafting techniques and depigmenting treatments. Surgery is best indicated for stable and localized forms of vitiligo, and only a small number of patients with vitiligo are considered suitable candidates. Treating vitiligo in the genital area with previously available therapies is not appropriate.

2.3. Clinical Efficacy and Safety Data With Ruxolitinib Cream

The results of 2 prospective identically designed confirmatory Phase 3 studies (INCB 18424-306 and INCB 18424-307) provide compelling evidence that treatment with ruxolitinib 1.5% cream BID provides clinically meaningful benefit (repigmentation) for adolescents and adults with vitiligo. Repigmentation of treated vitiligo lesions and superiority of ruxolitinib 1.5% cream BID over vehicle cream BID were observed for both studies, as demonstrated by statistically significant differences in response rates for F-VASI50/75/90, T-VASI50, and VNS scores of 4 or 5 at Week 24. Superiority of ruxolitinib 1.5% cream BID over vehicle cream BID was also observed for the mean percentage change from baseline in facial BSA at Week 24. The treatment effect on these variables was evident as early as Week 12 with continued improvement for participants randomized to ruxolitinib 1.5% cream BID through Week 52. Subgroup analyses demonstrated that the treatment effect of ruxolitinib 1.5% cream BID through 52 weeks of treatment was similar for adolescents (12 to < 18 years of age) and adults. A consistent treatment effect for F-VASI75 was also observed for all other subgroups evaluated.

Safety data from the confirmatory Phase 3 studies demonstrate that ruxolitinib 1.5% cream applied BID continuously for 52 weeks in adolescent and adult participants with vitiligo was safe and well-tolerated, with no meaningful differences in the safety profile of ruxolitinib cream for subgroups based on age, sex, race, or geographic region. The frequencies of Grade 3 or higher TEAEs, serious TEAEs, TEAEs leading to study drug interruption, and TEAEs leading to study drug discontinuation were low, and there were no deaths or TEAEs with a fatal outcome. The most frequently reported (≥ 2%) TEAEs during the 24-week, double-blind, vehicle-controlled period in participants treated with ruxolitinib 1.5% cream BID were application site acne, application site pruritus, nasopharyngitis, headache, COVID-19, upper respiratory tract infection, and sinusitis. These events, which were mostly nonserious, low grade, and resolved with no action taken with the study drug, remained the most frequently reported TEAEs with the addition of data from the 28-week treatment-extension period (ie, through Week 52). Exposure-adjusted incidence rates for each of these preferred terms were similar between the ruxolitinib 1.5% cream BID and vehicle cream treatment groups with the exception of application site acne. Of note, many of the events of application site acne did not recover/resolve, but participants continued on treatment without interrupting study drug in all cases but one.

2.4. Study Rationale

Patients with vitiligo with genital involvement have significant impact on their quality of life and sexual function (Silverberg and Silverberg 2013), and vitiligo treatments based on the most recent consensus guidelines (American Academy of Dermatology 2022, Gawkrodger et al 2008, Taieb et al 2013, Vitiligo Research Foundation 2022) are not appropriate for use in the genital area. In the 2 Phase 3 studies, approximately half of the participants had genital involvement; however, results regarding repigmentation specific to this region were not collected. As this is an area of particular concern for patients, this small, open-label study will focus on the efficacy and safety of ruxolitinib 1.5% cream BID for the treatment of vitiligo with genital involvement. Participants will be treated for up to 48 weeks, which is a reasonable treatment duration based on the results of previous studies. Recovery of pigment depends on a reservoir of melanocyte precursors to repopulate, which occurs over 6 to 8 weeks, and return functioning melanocytes to depigmented skin (≈ 4 weeks; Cichorek et al 2013), that is, the time course for repigmentation is tied to the time course for the resumption of melanogenesis. As such, repigmentation in vitiligo is generally recognized to be a slow biological process even with use of immune-modulating treatments.

2.5. Justification for Strength of Ruxolitinib Cream

Results from Study INCB 18424-211 showed that ruxolitinib 1.5% cream BID had the highest repigmentation rate on both F-VASI and T-VASI, particularly at Week 52. All ruxolitinib treatment strengths were generally safe and well-tolerated with no significant TEAEs or application site events and no clinically relevant hematological changes. Further, in the 2 Phase 3 studies (INCB 18424-306 and INCB 18424-307), ruxolitinib 1.5% cream BID showed statistically significant and clinically meaningful improvements for F-VASI and T-VASI compared with vehicle, and the safety profile was similar to that seen in the Phase 2 study.

2.6. Benefit/Risk Assessment

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

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

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

As ruxolitinib 1.5% cream is generally safe and well-tolerated and showed clear benefit for repigmentation in the Phase 2 and Phase 3 studies, overall benefit-risk assessment of ruxolitinib cream favors its use in adolescent and adult patients with vitiligo. Of note, in the 2 Phase 3 studies, approximately half of the participants had genital involvement; however, results specific to this region were not collected.

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

3. OBJECTIVES AND ENDPOINTS

Table 4 presents the objectives and endpoints.

Table 4: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of ruxolitinib cream in participants with genital vitiligo.	Proportion of participants achieving a genital VNS of "4 – A lot less noticeable" or "5 – No longer noticeable" at Week 48.
Secondary	
To evaluate the safety and tolerability of ruxolitinib cream.	Occurrence of AEs and changes in vital signs and laboratory data.
To further evaluate the efficacy of ruxolitinib cream.	• Proportion of participants achieving Genital-PhGVA of 0 or 1 at Week 48. • Change from baseline in affected BSA in the genital region at Weeks 24 and 48. • Proportion of participants achieving T-VASI50/75/90 at Weeks 24 and 48. • Proportion of participants achieving a genital VNS of "4 – A lot less noticeable" or "5 – No longer noticeable" at Week 24. • Proportion of participants in each category of the color-matching question at Weeks 24 and 48.

Table 4: Objectives and Endpoints (Continued)

Objectives	Endpoints
Exploratory	
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is an open-label study in which 45 participants with nonsegmental vitiligo with genital involvement will apply ruxolitinib 1.5% cream BID to all depigmented areas (up to 10% BSA) for up to 48 weeks (see Figure 1). In addition, a minimum of 15 participants must have Fitzpatrick skin types 4 to 6, with at least 10 participants having Fitzpatrick skin type 5 or 6. Participants should continue to treat depigmented areas identified for treatment at baseline regardless of whether the area begins to improve or fully repigment.

At any time during the study, if vitiligo areas become significantly more extensive than from the previous visit, the participant should contact the study site to discuss with the investigator whether additional evaluation at the clinic is required. Participants who have expansion of areas of vitiligo identified at baseline or develop new areas of vitiligo during the course of the treatment period may treat the additional areas of vitiligo with ruxolitinib cream as long as they do not exceed 10% BSA; these participants should have an unscheduled visit to document these changes. Additional areas of depigmentation should be captured in the EDC.

4.2. Overall Study Duration

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

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

4.3. Study Termination

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

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

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

1. Ability to comprehend and willingness to sign an ICF for the study.
2. Age ≥ 18 years at the time of signing the ICF.
3. Clinical diagnosis of nonsegmental vitiligo with genital involvement; the genital area (approximately 1% BSA) is defined as labia majora, labia minora, and perineum in females, and penis, scrotum, and perineum in males.
4. At least ≥ 0.25% BSA of nonsegmental vitiligo in the genital area.
5. Presence of pigmented hair within the depigmented areas (if the area is hair bearing).
6. At least 1 genital target lesion that is ≥ 0.1% BSA that has a pigmented hair within it.
7. Vitiligo on areas of the body besides the genitals.
8. Total body vitiligo area not exceeding 10% BSA.
9. Willing to have genital photography conducted.
10. Must 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.
11. Male and female participants must be willing to take appropriate contraceptive measures (see Appendix A) 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).

5.2. Exclusion Criteria

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

1. Other forms of vitiligo (eg, segmental) or other differential diagnosis of vitiligo or other skin depigmentation disorders (eg, balanitis xerotica obliterans, piebaldism, pityriasis alba, leprosy, postinflammatory hypopigmentation, progressive macule hypomelanosis, nevus anemicus, chemical leukoderma, and tinea versicolor).

2. Prior or current use of depigmentation treatments (eg, monobenzone).

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

3. Active or recurrent genital warts or herpes.
4. Male participants with partners with known current/active cervical intraepithelial neoplasia or anal intraepithelial neoplasia.
5. An active sexually transmitted disease, sexually transmitted infection, or other skin disorder affecting the genital area (eg, scabies, fungal infection, molluscum).
6. Had ≥ 3 laser hair removal treatments in an area to be treated for vitiligo.
7. No venous access outside of areas to be treated.
8. Concurrent conditions and history of other diseases as follows:
   a. Any other skin disorder that, in the opinion of the investigator, would interfere with the study medication application or study assessments.
   b. Immunocompromised (eg, lymphoma, acquired immunodeficiency syndrome, or Wiskott-Aldrich syndrome).
   c. Chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before baseline.
   d. Active acute bacterial, fungal, or viral skin infection (eg, herpes simplex, herpes zoster, chicken pox, clinically infected atopic dermatitis, or impetigo) within 1 week before baseline.
   e. Unstable asthma or COPD requiring systemic treatment (such as intravenous steroids) or hospital admission or emergency room treatment within 6 months from baseline; or stable asthma or COPD requiring more than 880 µg/day of inhaled budesonide or equivalent high dose of other inhaled corticosteroids.
   f. Current or history of hepatitis B or C virus infection.
   g. Current or history of HIV infection.
9. Any serious illness or medical, physical, or psychiatric condition(s) that, in the investigator's opinion, would interfere with full participation in the study, including application of study cream and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data. For example:
   a. Clinically significant or uncontrolled cardiovascular disease, including unstable angina, acute myocardial infarction, or stroke within 6 months from Day 1 of study cream application, New York Heart Association Class III or IV congestive heart failure, and arrhythmia requiring therapy or uncontrolled hypertension (blood pressure > 150/90 mmHg) unless approved by medical monitor/sponsor.
   b. Participants with or a history of malignancy in the 5 years preceding the baseline visit, except for adequately treated, nonmetastatic, nonmelanoma, skin cancer.
   c. Current and/or history of arterial or venous thrombosis, including deep venous thrombosis and pulmonary embolism.
   d. Current and/or history of active tuberculosis; or current and/or history of latent tuberculosis unless adequately treated.
   e. History of severe anemia, severe thrombocytopenia, or severe neutropenia.

10. Any of the following clinical laboratory test results at screening:
    a. Hemoglobin < 100 g/L (ie, 10 g/dL)
    b. Absolute neutrophil count < 1.5×10^9/L (ie, 1500/μL)
    c. Platelet count < 1×10^{11}/L (ie, 100,000/μL)
    d. AST or ALT ≥ 2.5 × ULN
    e. Total bilirubin > 1.5 × ULN unless Gilbert's syndrome
    f. Estimated glomerular filtration rate < 60 mL/min/1.73 m^2 (using the Chronic Kidney Disease Epidemiology Collaboration equation)
    g. Any other clinically significant laboratory result that, in the opinion of the investigator, poses a significant risk to the participant
11. Use of any of the following treatments within the indicated washout period before baseline:
    a. **1 week:** Topical drugs when used on the vitiligo areas (eg, corticosteroids, calcineurin, bimatoprost, phosphodiesterase type 4 inhibitors, retinoids).
    b. **4 weeks:**
       – Melanocyte-stimulating agents (eg, afamelanotide).
       – Immunomodulating systemic medications (eg, corticosteroids, methotrexate, cyclosporine).
       – Live vaccines.
         Note: Live-attenuated vaccines are prohibited during the course of the study and within 4 weeks after the EOT visit.
    c. **12 weeks:**
       – JAK inhibitors, systemic or topical.
       – 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.
12. Body mass index < 17 or > 40 kg/m^2.
13. Pregnant or lactating participants, or those considering pregnancy during the period of their study participation.
14. 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 application schedule and study assessments.
15. Current treatment or treatment within 30 days or 5 half-lives (whichever is longer) before the baseline visit with another investigational medication or current enrollment in another investigational drug study.
16. Committed to a mental health institution by virtue of an order issued either by the judicial or the administrative authorities.

17. In the opinion of the investigator, unable or unlikely to comply with the application schedule and study evaluations.
18. Employees of the sponsor or investigator or are otherwise dependents of them.
19. Known allergy or reaction to any component of the study drug formulation.

5.3. Lifestyle Considerations

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

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

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

Participants should not wax the genital area during the study.

Men should not have sexual intercourse within 4 hours of application of ruxolitinib cream to the genital area.

Men applying ruxolitinib cream to the shaft of the penis should use a condom when having sexual intercourse (vaginal or anal).

5.4. Screen Failures

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

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

5.5. Replacement of Participants

Participants will not be replaced during the study.

6. STUDY TREATMENT

6.1. Study Treatment Administered

Table 5 presents the study treatment information. Participants should apply study cream only to depigmented vitiligo areas identified by the investigator at baseline up to a BSA of ≤ 10%. Participants should continue to treat all depigmented vitiligo areas identified for treatment at baseline regardless of whether the area begins to improve or fully repigment.

On visit days, study cream will be applied during the visit to the non–genital areas in the presence of study staff; study cream will also be applied to genital areas during the visit, but the presence of study staff is not required. Participants should remove study cream from the tube in fingertip units until all of the areas to be treated are covered by a thin film. The tube will be weighed before and after application to determine the participant's dose. Participants will be instructed to document the treated areas and be advised to limit use to no more than 1 tube (60 g) per week. Application instructions will be provided by the site study staff, and the participants will record their daily applications via a diary card given to the participants during each study visit. Refer to the Study Pharmacy Manual for participant instructions for handling of study cream.

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

Table 5: Study Treatment Information (Ruxolitinib Cream)

Study treatment name:	Ruxolitinib
Dose formulation:	Cream
Unit strength:	1.5%
Route of administration:	Topical
Application instructions:	BID. A thin film is applied to depigmented vitiligo areas up to a maximum of 10% BSA.
Packaging and labeling:	Ruxolitinib cream will be provided in 60-g tubes. Each tube will be labeled per country requirements.
Storage:	Ambient (15°C-30°C/59°F-86°F)
Status of treatment in participating countries:	Approved (US) and investigational (all other countries)

6.2. Preparation, Handling, and Accountability

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

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

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

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

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

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

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study cream until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee the destruction of any remaining study cream according to institutional SOPs. If, however, local procedures do not allow on-site destruction, shipment of the study cream back to the sponsor is allowed. In this case, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study cream is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

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

Instructions for the participants for handling ruxolitinib cream can be found in Appendix B.

6.3. Measures to Minimize Bias: Randomization and Blinding

Not applicable as this is an open-label study.

6.4. Study Treatment Compliance

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

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

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

6.5. Dose Modifications

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

6.5.1. Criteria and Procedures for Application Interruptions of Study Cream

In some circumstances, it may be necessary to interrupt application of ruxolitinib cream temporarily. Except in cases of emergency, it is recommended that any findings of concern (eg, AEs) be confirmed and that the investigator consult with the sponsor medical monitor (or other representative of the sponsor) before interrupting study cream. Additionally, the investigator must obtain approval from the sponsor before restarting study cream. Participants who have a recurrence of the initial AE upon restarting the study cream, and the AE is confirmed related to the study cream, may need the study cream to be permanently discontinued (see Section 6.5.2).

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

Instructions for application interruptions for ruxolitinib cream are outlined in Table 6. Individual decisions regarding interruptions should be made using clinical judgment in consultation with the medical monitor (whenever possible), taking into account relatedness of the AE to the study treatment and the participant's underlying condition.

Table 6: Guidelines for Interruption and Restarting of Study Cream

Adverse Event	Action Taken
ALT or AST > 3 × ULN	• Laboratory abnormalities should be confirmed with repeat testing within 48 hours whenever possible and immediate delivery of the laboratory results requested. • Study cream applications must be interrupted. At the discretion of the investigator, after consultation with the sponsor, study cream application may be resumed once these have resolved to baseline levels.
Any other Grade 3 or higher laboratory abnormality, with the exception of asymptomatic elevations in triglyceride, cholesterol, or amylase	
Any Grade 4 laboratory abnormality or AST or ALT > 5 × ULN	• Laboratory abnormalities should be confirmed with repeat testing within 48 hours whenever possible and immediate delivery of the laboratory results requested. • Discontinue study cream if laboratory abnormalities are confirmed.

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

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

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

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 medication or procedure received up to 12 weeks before baseline through 30 days after the last application of study cream will be recorded in the eCRF. Any addition, deletion, or change in the dose of these medications will also be recorded.

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

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

6.6.1. Permitted Medications and Procedures

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

- Participants may use bland emollients or camouflage makeups.

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

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

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

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

6.6.2. Restricted Medications and Measures

The following are restricted during the study under specified conditions:

- Use of any over-the-counter, nonprescription preparations (including vitamins, minerals, and phytotherapeutic, herbal, or plant-derived preparations) within 7 days before the baseline visit through the safety follow-up visit, unless deemed acceptable by the investigator.
- Use of any prescription medication (including immunizations and phytotherapeutic, herbal, or plant-derived preparations) within 7 days before the baseline visit through the safety follow-up visit, unless deemed acceptable by the investigator.
- Baths or showers within 2 hours after study cream application.
- Treatment for dermatologic disease besides vitiligo (eg, AD or psoriasis) is allowed for areas not being treated for vitiligo if:
  - It involves < 10% of the BSA outside of the areas treated for vitiligo.
  - Topical tacrolimus, pimecrolimus, or corticosteroids Class 6 or 7 (or low potency per WHO classification; see Appendix D) are at a stable dose.
  - Topical corticosteroids Class 1 through 5 (see Appendix D) are used for no longer than 7 sequential days and no more than 14 days in total.
- Use of oral corticosteroids for no longer than 7 days if deemed acceptable by the investigator and the sponsor for nondermatologic conditions (eg, asthma exacerbation, bronchitis).

6.6.3. Prohibited Medications and Procedures

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

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

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

6.7. Treatment After the End of the Study

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

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

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

- The participant becomes pregnant.
- Consent is withdrawn.
  Note: Consent withdrawn means that the participant has explicitly indicated that they do not want to be followed any longer; in this case, no further data (except data in public domain) may be solicited from or collected regarding the participant. Participants may choose to discontinue application of study cream and remain in the study to be followed for safety.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- Any AE of unacceptable severity as noted in Section 6.5.2.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

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

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

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the application of study cream, the ET visit should be conducted. Reasonable efforts should be made to have the participant return for the safety follow-up visit. These visits are described in Table 3. The last date of the last application of study cream and the reason for discontinuation of study cream will be recorded in the eCRF.

If a participant is discontinued from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for discontinuation must be documented in the participant's medical record, and the primary reason for discontinuation must be included in the eCRF.
- The ET visit should be performed.

- The date of the ET visit should be recorded in the eCRF.
- The status of the participant should be updated in the IRT.
- Participants must be followed for safety until the time of the safety follow-up visit or until study cream–related AEs resolve, return to baseline, or are deemed irreversible, whichever is longest.

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

7.2. Participant Withdrawal From the Study

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

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

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

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

7.3. Lost to Follow-Up

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

8. STUDY ASSESSMENTS AND PROCEDURES

See Appendix C for COVID-19–related guidance.

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

- The investigator or their representative will explain the nature of the study to the participant or their legally authorized representative and answer all questions regarding the study.
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.
  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the participant. An ICF template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to participant records.
  - The ICF must contain all required elements and describe the nature, scope, and possible consequences of the study in a form understandable to the study participant.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the countries in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that their personal data collected for the study will be used by the sponsor and/or their designee(s) in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must provide consent to the most current version of the ICF during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

8.1.2. Screening Procedures

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

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

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

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

8.1.3. Interactive Response Technology Procedure

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

8.1.4. Distribution of Study Reminder Cards and Diaries

Starting at the Day 1 visit, and at each visit indicated in Table 3 thereafter, a study cream–specific diary will be used by each participant to record use of the study cream. The completed diary will be reviewed during each of the participant's visits.

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

Participants will be provided with a reminder card starting on Day 1 and at all visits (through Week 48). The reminder card will indicate the date/time of the next visit and will remind the participant that they should apply study cream under site supervision at the clinic during the visit 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 and surgical treatments within the last 2 years that are considered to be clinically significant by the investigator. If relevant to an AE that occurs during the study, additional medical history may be collected.

8.1.5.2. Disease Characteristics and Treatment History

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

8.2. Efficacy Assessments

8.2.1. Body Surface Area

The BSA depigmented by vitiligo will be estimated at each visit as indicated in Table 3. Body surface area assessments will be performed using the palmar method and 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.

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

In addition, the BSA depigmented by vitiligo will be assessed for the face (which represents up to 3% of the head/neck) and the genitals (which represents approximately 1% of the trunk).

Facial BSA takes into account the depigmented areas of the forehead to the original hairline, the cheek vertically to the jawline and laterally from the corner of the mouth to the tragus, the nose, and the eyelids. The face will not include surface area of the lips, scalp, ears, or neck.

Genital BSA takes into account the depigmented areas of the labia majora, labia minora, and perineum in females and the penis, scrotum, and perineum in males.

8.2.2. Vitiligo Area Scoring Index

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

the following percentages: 0, 10%, 25%, 50%, 75%, 90%, or 100%. At 100% depigmentation, no pigment is present; at 90%, specks of pigment are present; at 75%, the depigmented area exceeds the pigmented area; at 50%, the depigmented and pigmented area are equal; at 25%, the pigmented area exceeds the depigmented area; and at 10%, only specks of depigmentation are present. Data will be collected so that VASI scores can be calculated for each of the 6 body regions noted for the total BSA as well as for the face and the genitals.

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

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

The components to calculate VASI (BSA and percentage depigmentation) will be assessed at visits listed in Table 3. Full details on the conduct of these assessments will be provided in the Study Manual.

8.2.3. Target Lesion

Participants must have at least 1 genital target lesion that is ≥ 0.1% BSA that has a pigmented hair within it at screening and baseline. The longest diameter will be measured in millimeters as well as the measurement perpendicular to the longest diameter. This lesion will be assessed and measured at each subsequent visit. Additionally, photography will be employed at the timepoints specified in Table 3 to track the response of the lesion to topical drug. A note should be made and baseline photographs can be marked with the location of the target lesion.

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 (see Table 7). Response will be reported for total body (T-PhGVA). The T-PhGVA will be performed as indicated in Table 3.

Table 7: 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. Physician's Global Vitiligo Assessment (Genital)

The severity of genital vitiligo will be assessed by the physician using the PhGVA, which has a 5-point scale (see Table 8). Response will be reported for genital region (Genital-PhGVA). The Genital-PhGVA will be performed as indicated in Table 3.

Table 8: Genital 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, shaft of penis or labia minora)
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

8.2.6. Photography

Photography of the genital area and the target lesion will be obtained at visits listed in Table 3. All sites will use 2-dimensional photography.

8.2.7. Patient-Reported Outcomes

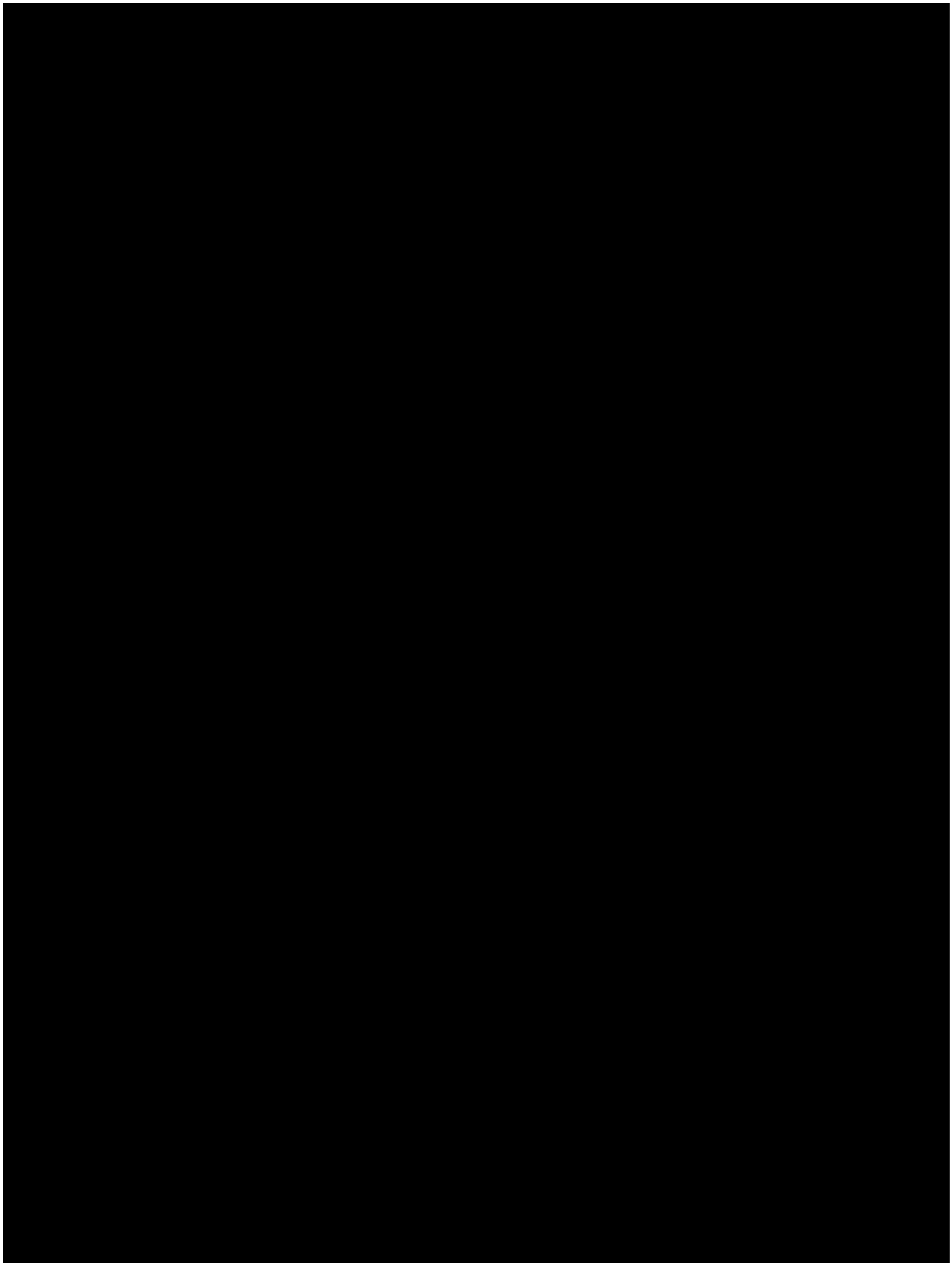
Patient-reported outcomes and quality of life will be assessed at the visits noted in Table 3 using the following tools:

[redacted]

In order to avoid bias in the participants' responses to the questionnaires, the 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 PROs must be completed before the participant's first application of study cream.

[redacted]



[redacted]

8.2.8. Health Economics

Health economics parameters are not evaluated in this study.

8.3. Safety Assessments

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

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

8.3.1. Adverse Events

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

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

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

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

8.3.2. Physical Examinations

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

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

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

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

8.3.3. Vital Signs

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

Vital sign measurements (to be taken before blood collection for laboratory tests) include blood pressure, pulse, respiratory rate, and body temperature. If vital signs cannot be taken before blood collection for laboratory tests, there should be a minimum of 30 minutes from the completion of the blood collection procedures to the beginning of the vital signs collection. Blood pressure and pulse will be taken with the participant in the recumbent, semirecumbent, or sitting position after 5 minutes of rest. Any abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

8.3.4. Electrocardiograms

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

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

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

8.3.5. Laboratory Assessments

Required laboratory tests are listed in Table 9. See Table 3 for timing of assessments. Clinical laboratory assessments will be performed at a central laboratory (refer to the Laboratory Manual for sample handling and shipping instructions).

Clinically significant abnormal laboratory findings are those that induce clinical signs or symptoms, require concomitant therapy, or require changes in application of study cream. All laboratory tests with values considered clinically significantly abnormal during participation in

the study, or within 30 days after the last application of study cream, should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

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

Table 9: Required Laboratory Analytes

Serum Chemistries[a]	Hematology	Urinalysis	Pregnancy Testing
Albumin Alkaline phosphatase ALT AST Bicarbonate or CO_2 Blood urea nitrogen or urea Calcium Chloride Creatine kinase Creatinine Glucose Lactate dehydrogenase Phosphate Potassium Sodium Total bilirubin Direct bilirubin (if total bilirubin is elevated above ULN) Total protein	Complete blood count, including: • Hemoglobin • Hematocrit • Mean corpuscular volume • Platelet count • Mean platelet volume • Red blood cell count • Reticulocyte count • White blood cell count Differential count, including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein Note: Abnormal results should be microscopically examined.	Human chorionic gonadotropin (urine and serum) **Other** FSH[b] Free T4 Thyroid-stimulating hormone

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

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

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

8.3.5.1. Pregnancy Testing

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

If a pregnancy is confirmed by a serum pregnancy test, see Section 9.8 for reporting requirements.

8.5. Pharmacodynamic and Translational Assessments

Pharmacodynamic parameters will not be evaluated in this study.

8.6. Unscheduled Visits

Unscheduled visits may occur at any time at the investigator's discretion. Appropriate clinical and laboratory tests may be performed, as clinically indicated. Also, if a participant has an expansion from baseline of their vitiligo, an unscheduled visit should occur to document the additional areas.

8.7. Early Termination

If a decision is made that the participant will permanently discontinue application of study cream, the ET visit should be conducted. If the ET visit coincides with a regular study visit, then the ET evaluations will supersede those of that scheduled visit, and the data should be entered in the ET 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 ET procedures completed.

8.8. Safety Follow-Up

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

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

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

9.1. Definition of Adverse Event

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

9.2. Definition of Serious Adverse Event

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

A serious adverse event is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an adverse drug experience that places the participant, in the opinion of the initial reporter, at immediate risk of death from the adverse experience as it occurs. This does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (involving at least an overnight stay) at the hospital or emergency department for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment or planned surgery (eg, stent replacement, hip surgery) is not considered an SAE. Hospitalization for medical interventions in which no unfavorable medical occurrence occurred (ie, elective procedures or routine medical visits) is not considered an SAE.
d. Results in persistent or significant disability/incapacity The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is an important medical event An important medical event is an event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such events include new invasive or malignant cancers, intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization; development of drug dependency or drug abuse. Secondary malignancies should always be considered SAEs**.**

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

Adverse Event and Serious Adverse Event Recording

- An AE/SAE that begins or worsens after informed consent is signed should be recorded on the Adverse Events Form in the eCRF. All AEs/SAEs should be reported for enrolled participants, but only SAEs need to be reported for screen failure participants. For enrolled participants, conditions that were present at the time informed consent was given should be recorded on the Medical History Form in the eCRF. For detailed information, refer to the eCRF guidelines.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator (or designee) will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completing the Adverse Events Form in the eCRF.
- There may be rare instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted by the site staff on the copies of the medical records before submission. These records can be submitted to Incyte Pharmacovigilance by email/fax per the contact information listed in the Study Reference Manual or as per SAE completing guidelines.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE/SAE.

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

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

Assessment of Intensity

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

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

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

Assessment of Causality

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

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

9.4. Reporting of Serious Adverse Events

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

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

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

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

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

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

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

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

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

Serious Adverse Event Reporting

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

9.5. Potential Drug-Induced Liver Injury

In the event a participant has 1) an increase in ALT or AST elevation ≥ 3 × ULN, 2) a total bilirubin ≥ 2 × ULN, and 3) an ALP < 2 × ULN, clinical tests (eg, blood and imaging tests) must be performed frequently as per standard of care until resolution and/or stabilization. In addition, a diagnostic workup must be performed to exclude alternative causes such as viral hepatitis, pre-existing chronic or acute liver disease, the administration of other drug(s) known to be hepatotoxic, or confirmed Hy's law.

Follow the SAE and follow-up reporting requirements per Section 9.2 as potential drug-induced liver injury AEs may be potential SAEs classified in the category of important medical event.

9.6. Events of Clinical Interest

Not applicable.

9.7. Emergency Unblinding of Treatment Assignment

Not applicable.

9.8. Pregnancy

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

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

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

Any SAE occurring during the pregnancy of a study participant must be recorded and reported as described in Section 9.4.

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.

9.9. Warnings and Precautions

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

9.10. Product Complaints

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

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

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

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

9.11. Treatment of Overdose

There has been no clinical experience with overdose of ruxolitinib cream. Overdose with ruxolitinib cream is unlikely. If too much is applied, the excess can be wiped off.

10. STATISTICS

10.1. Sample Size Determination

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

10.2. Populations for Analysis

The populations for analysis are provided in Table 10.

Table 10: Populations for Analysis

Population	Description
FAS	The FAS includes all participants enrolled in the study who applied ruxolitinib cream at least once. The FAS will be used for the summary of demographics, baseline characteristics, participant disposition, and analyses of all efficacy and safety data.
[redacted]	

10.3. Level of Significance

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

10.4. Statistical Analyses

10.4.1. Efficacy Analyses

All efficacy assessments will be summarized using descriptive statistics by visit for the FAS.

10.4.1.1. Analysis of Primary Efficacy Endpoint

The primary endpoint is the proportion of participants achieving a genital VNS of "4 – A lot less noticeable" or "5 – No longer noticeable" at Week 48. Summary statistics will include sample size, frequency, percentage and standard error of percentage, and the 95% CI.

10.4.1.2. Analysis of Secondary Efficacy Endpoints

10.4.1.2.1. Continuous Efficacy Endpoints

For continuous measurements, by-visit summary statistics, including actual measurement, change from baseline, and percentage change from baseline, will be presented.

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

10.4.1.2.2. Categorical Efficacy Endpoints

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

10.4.2. Safety Analyses

Safety is being evaluated as a secondary objective in this study. Safety analyses will be conducted using the safety population and are summarized in Table 11.

Table 11: Safety Analyses

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

10.4.3. Other Analyses

[redacted]

10.5. Interim Analysis

No formal interim analysis is planned in this study.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

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

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

11.1.1. Identification of the Coordinating Principal Investigator

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

11.2. Data Management

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

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

The sponsor (or designee) will be responsible for the following:

- 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 the following:

- Recording, or ensuring the recording of, all relevant data relating to the study in the eCRF.
- Delivering, or ensuring the delivery of, all other results, documents, data, know-how, or formulas relating to the study to the sponsor or designee electronically and/or centrally (eg, laboratory data, imaging data, biomarker data, photographs, diary data) or as otherwise specified in the Protocol.

- Maintaining adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source data are, in general, all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
- Verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Maintaining accurate documentation (source data) that supports the information entered in the eCRF, sent to a central vendor designated by the sponsor, or as described in other study and data flow manuals.
  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed and available at the investigator's site. Examples of source documents are original documents, data, and records (eg, hospital records; electronic hospital records; clinical and office charts; laboratory notes; memoranda; participants' diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives; microfilm or magnetic media; x-rays; participants' files; and e-records/records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).
  - Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current applicable medical records must be available.
- Sending participants' data, either as unique samples, copies, or photographs, to be evaluated centrally or analyzed centrally, or both, by a qualified vendor designated by the sponsor.
  - As required by privacy and data protection regulations and Incyte's privacy policies, if any photographs of participants are to be taken, the photographs must be limited to the area of the face or the body that is strictly necessary and the photographs should be masked (ie, identifying features such as eyes, mouth, scars, tattoos, or unique markings or features should be either obscured with a black bar or digitally pixelated so as to not permit the reidentification of the participants and preserve their confidentiality) by a specially designated photography vendor prior to sending the photographs to Incyte or any other third-party vendors for analysis or further processing.

- 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 Quality Assurance

The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations). The sponsor or designee is responsible for the data management of this study, including quality checking of the data. Further, monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues, Protocol deviations, and monitoring techniques (eg, central, remote, or on-site monitoring) are provided in the Monitoring Plan.

Quality tolerance limits will be predefined to identify systematic issues that can impact participants' safety, efficacy results and analysis, and/or reliability of study results. These predefined parameters will be monitored during the study and can be adjusted during the study upon data review. Important deviations from the quality tolerance limits and remedial actions taken, including reporting to IRBs/IECs and health authorities if applicable, will be summarized in the CSR.

11.4. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data protection laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that personal information is handled in accordance with local data protection laws (including but not limited to HIPAA and GDPR) as applicable, and the sponsor operates comprehensive data privacy and data security programs that are applicable to this study. Appropriate notice, or notice and consent (as may be required by each applicable jurisdiction), for collection, use, disclosure,

and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws. Appropriate data protection terms that comply with applicable laws will be included in relevant study agreements.

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

In the event of a data breach involving participant data, the sponsor or its designee will follow the sponsor's incident response procedures. The precise definition of a data breach varies in accordance with applicable law but may generally be understood as a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data. In accordance with its incident response procedures, the sponsor will assess the breach to consider its notification and remediation obligations under applicable law.

11.5. Financial Disclosure

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

Any new clinical investigators added to the covered clinical study during its conduct must also submit a completed Clinical 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.

11.6. Publication Policy

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

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

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

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

11.7. Study and Site Closure

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

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

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

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

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS AND DEFINITIONS

Definitions

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

Women in the following categories are not considered WOCBP:

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

For male participants of reproductive potential[b]

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

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

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

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

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

For female participants who are WOCBP

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

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

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

APPENDIX B. INSTRUCTION TO PARTICIPANTS FOR HANDLING RUXOLITINIB CREAM

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

- Store study cream at room temperature.
- Make every effort to apply study cream on schedule.
- Report any missed applications.
- Keep study cream in a safe place and out of reach of children.
- Bring all used and unused study cream tubes to the site at each visit.
- Remove study cream from the tube in fingertip units until all of the areas to be treated are covered by a thin film.
- Do not apply study cream on visit days as it will be applied at the site under supervision of the site staff.
- Do not use more than 1 tube (60 g) per week.
- Do not use emollients, sunscreen, or camouflage makeups within 2 hours after study cream application.
- Do not apply study cream over sunscreen or camouflage makeup. These must be removed from the skin before application of the study cream. Any makeup remover must then be washed off and the skin dried before application of the study cream.
- Do not take baths or showers within 2 hours after study cream application.
- Female participants: Keep the genital area free of liquids and avoid wiping the area for as long as possible after application of study cream.
- Male participants: Do not have sexual intercourse for at least 4 hours after application of study cream to the genital area.
- Male participants: If you apply study cream to the shaft of the penis, you should use a condom when having sexual intercourse (vaginal or anal).

APPENDIX C. COVID-19 PANDEMIC MITIGATION STRATEGIES AND INSTRUCTIONS

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

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

Study Site Visits

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

- In order to minimize participant risk, study visits (except Day 1, Week 4, Week 12, and Week 48 visits) may be conducted via telemedicine modalities (phone or video). At a minimum, a review of AEs, concomitant medications, and study cream compliance must be completed. Periodic on-site visits should be conducted whenever feasible. The physician efficacy assessments must not be conducted by phone or video.
- Day 1, Week 4, Week 12, and Week 48 visits must be conducted in person in their entirety because PK and physician efficacy assessments must be conducted in person. These visits cannot be missed or conducted remotely. The investigator should document visit-window deviations in the eCRF if necessary. If an out-of-window deviation is significant (ie, > 4 weeks out-of-window), the investigator should contact the sponsor for discussion and further instructions.

Investigational Medicinal Product Dispensing and Distribution

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

Clinical Trial Monitoring

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

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

APPENDIX D. WHO CLASSIFICATION OF TOPICAL CORTICOSTEROIDS

Hydrocortisone and betamethasone are examples of low- and high-potency topical corticosteroids. Topical corticosteroids have been ranked in terms of potency into 4 groups consisting of 7 classes. Class I topical corticosteroids are the most potent, and Class VII are the least potent. Efficacy and side effects are greatest with the Class I ultra-high–potency preparations, which should only be used for limited time periods (1-2 weeks). Representative preparations by group are listed in the table below. These groups may vary depending on the formulation and concentration and should be considered approximate. In general, ointments are more potent than creams or lotions. Potency is also increased when topical corticosteroids are used under occlusive dressings or in intertriginous areas.

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

Source: WHO 1997.

APPENDIX E. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1	28 FEB 2023

Amendment 1 (28 FEB 2023)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to add 15 participants and add minimums for Fitzpatrick skin types 4 to 6.

1. **Section 1, Protocol Summary (Table 2: Key Study Design Elements); Section 4.1, Overall Design**

   Description of change: Added 15 participants to the study.

   Rationale for change: Adding an additional country.

2. **Section 1, Protocol Summary; Section 4.1, Overall Design**

   Description of change: Added a minimum number of participants with Fitzpatrick skin types 4, 5, and 6.

   Rationale for change: To allow a better representation of the population of patients affected by vitiligo.

3. **Incorporation of administrative changes.** Other regulatory guidance and administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

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Approval Task	[redacted] Approver [redacted] IAI 28-Feb-2023 19:26:14 GMT+0000
Approval Task	[redacted] Document Preparer [redacted] Clinical Research Scientist 28-Feb-2023 19:59:22 GMT+0000
Approval Task	[redacted] Approver [redacted] Biostatistics 28-Feb-2023 20:51:06 GMT+0000
Approval Task	[redacted] Approver [redacted]of Inflammation and AutoImmunity Group 28-Feb-2023 21:14:55 GMT+0000
Approval Task	[redacted] [redacted] Clinical Operations 01-Mar-2023 04:46:13 GMT+0000

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