Official Title: **A Randomized, Double-Blind, Dose-Ranging Study of INCB018424 Phosphate Cream in Subjects With Vitiligo**

NCT Number: NCT03099304

Document Date: Clinical Study Protocol Version 3: 01 August 2019

Clinical Study Protocol

INCB 18424-211

A Randomized, Double-Blind, Dose-Ranging Study of INCB018424 Phosphate Cream in Subjects With Vitiligo

Product:	**INCB018424 Phosphate Cream**
IND Number:	**77,101**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol (Version 0):	**20 JAN 2017**
Amendment (Version) 1:	**17 MAY 2017**
Amendment (Version) 2:	**08 JAN 2018**
Amendment (Version) 3:	**01 AUG 2019**

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and conducted in adherence to the study Protocol, Good Clinical Practices as defined in Title 21 of the US Code of Federal Regulations Parts 11, 50, 54, 56, and 312, as well as ICH GCP consolidated guidelines (E6) and applicable regulatory requirements.

INVESTIGATOR'S AGREEMENT

I have read the INCB 18424-211 Protocol Amendment 3 (Version 3 dated 01 AUG 2019) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

(Printed Name of Investigator)

(Signature of Investigator) (Date)

SYNOPSIS

Name of Investigational Product: INCB018424 Phosphate Cream (hereafter referred to as INCB018424 cream)

Title of Study: A Randomized, Double-Blind Dose-Ranging Study of INCB018424 Phosphate Cream in Subjects With Vitiligo

Protocol Number: INCB 18424-211	**Study Phase:** 2

Indication: Vitiligo

Primary Objective:

- To establish the efficacy of 24 weeks of treatment with INCB018424 cream in subjects with vitiligo.

Secondary Objectives:

- To estimate the dose-response relationship of INCB018424 cream at Weeks 24 and 52.
- To evaluate the safety and tolerability of INCB018424 cream in subjects with vitiligo.

Primary Endpoint:

- Proportion of subjects treated with INCB018424 cream who achieve a ≥ 50% improvement from baseline in Face Vitiligo Area Severity Index score (F-VASI50) at Week 24 compared with subjects treated with vehicle.

Key Secondary Endpoints:

- Proportion of subjects who achieve a Physician Global Vitiligo Assessment (PhGVA) on the face (F-PhGVA) of clear or almost clear at Week 24.
- Proportion of subjects who achieve a ≥ 50% improvement from baseline in Total Vitiligo Area Severity Index score (T-VASI50) at Week 52.

Overall Study Design:

This is a 3-part, randomized, double-blind, and vehicle-controlled study in subjects with vitiligo who have depigmented areas including at least 0.5% of the total BSA on the face and at least 3% of the total BSA on nonfacial areas as determined by the palmar or handprint (palm plus 5 digits) method. Approximately 150 subjects, aged 18 to 75 years, will be randomized to 1 of 4 dose strengths of INCB018424 cream (1.5% BID, 1.5% QD, 0.5% QD, 0.15% QD) or vehicle in a 1:1:1:1:1 ratio and stratified by age (≤ 30 or > 30 years).

The 3 parts of the study include a 24-week, double-blind, vehicle-controlled treatment period; a 28-week, continued, double-blind treatment period; and a 104-week, open-label extension period. After completion of the Week 24 assessments, subjects randomized to vehicle will be randomized to 1 of the 3 higher active treatment groups in a 1:1:1 ratio while maintaining the blind. Subjects in the 0.15% QD dose group who do not achieve a ≥ 25% improvement from baseline on F-VASI will be re-randomized to 1 of the 3 higher active treatment groups while maintaining the blind. Subjects randomized to INCB018424 0.15% QD who achieve a ≥ 25% improvement from baseline on F-VASI will remain on the same dose until Week 52. Subjects randomized to INCB018424 1.5% BID, 1.5% QD, and 0.5% QD will remain on the same dose until Week 52.

After completion of the Week 52 assessments, subjects who continue to be eligible for the study will be offered the opportunity to receive an additional 104 weeks of open-label treatment with INCB018424 1.5% cream BID. In the open-label extension, subjects may be offered low-dose narrow band-UVB phototherapy in addition to INCB018424 cream in consultation with the investigator and

sponsor. Subjects who are eligible for the open-label extension who have complete facial repigmentation (F-PhGVA score of 0) may stop applying study drug to the face, decrease the application rate to QD, or continue BID based on investigator judgement at Weeks 52 and 80 (after Week 80, subjects may also be permitted to modify their treatment regimen after the investigator has consulted with the sponsor).

Study Population:

Male or female subjects, aged 18 to 75 years, who have been diagnosed with vitiligo with depigmented areas including at least 0.5% of the total BSA on the face and at least 3% of the total BSA on nonfacial areas will be eligible for the study.

Key Inclusion Criteria:

A subject who meets all of the following criteria may be included in the study:

- Male or female subjects aged 18 to 75 years, inclusive.
- Subjects with a clinical diagnosis of vitiligo.
- Subjects with vitiligo with depigmented areas including:
  - at least 0.5% of the total BSA on the face (0.5% BSA is approximately equal to the area of the subject's palm [without digits]) AND
  - at least 3% of the total BSA on nonfacial areas (3% BSA is approximately equal to the area of 3 of the subject's handprints [palm plus 5 digits]).
- Subjects who agree to discontinue all agents used to treat vitiligo from screening through the final follow-up visit. Over-the-counter preparations deemed acceptable by the investigator and camouflage makeups are permitted.

Key Exclusion Criteria:

A subject who meets any of the following criteria will be excluded from the study:

- Conditions at baseline that would interfere with evaluation of vitiligo.
- Subjects who are receiving any kind of phototherapy, including tanning beds.
- Subjects with other dermatologic disease besides vitiligo whose presence or treatments could complicate the assessment of repigmentation.
- Subjects who have used skin bleaching treatments for past treatment of vitiligo or other pigmented areas.
- Subjects who have received any of the following treatments within the minimum specified timeframes.
  - Use of any biologic, investigational, or experimental therapy or procedure for vitiligo within 12 weeks or 5 half-lives (whichever is longer) of screening. Investigational biologics should be discussed with the sponsor to determine if a longer period of discontinuation is required.
  - Use of laser or light-based vitiligo treatments, including tanning beds, within 8 weeks of screening.
  - Use of immunomodulating oral or systemic medications (eg, corticosteroids, methotrexate, cyclosporine) or topical treatments that may affect vitiligo (eg, corticosteroids, tacrolimus/pimecrolimus, retinoids) within 4 weeks of screening.
- Use of any prior and concomitant therapy not listed above that may interfere with the objective of the study as per discretion of the investigator, including drugs that cause photosensitivity or skin pigmentation (eg, antibiotics such as tetracyclines, antifungals) within 8 weeks of screening.
- Subjects with a clinically significant abnormal TSH or free T4 at screening as determined by the investigator.
- Subjects with cytopenias at screening, defined as follows:
  - Leukocytes $< 3.0 \times 10^9$/L ($< 2.5 \times 10^9$/L for subjects who are African-American).
  - Neutrophils < lower limit of normal.

- Lymphocytes < 0.8×10^9/L.
- Hemoglobin < 10 g/dL.
- Platelets < 100×10^9/L.

- Subjects with severely impaired liver function (Child-Pugh Class C) or alanine aminotransferase or aspartate aminotransferase ≥ 1.5 × upper limit of normal on repeated assessment.
- Subjects with impaired renal function with estimated creatinine clearance less than 60 mL/min.
- Positive serology test results for HIV, for hepatitis B surface antigen or core antibody, or for hepatitis C virus antibody with detectable RNA at screening.
- Subjects taking potent systemic cytochrome P450 3A4 inhibitors or fluconazole within 2 weeks or 5 half-lives, whichever is longer, before the baseline visit.
- Subjects who have previously received JAK inhibitor therapy, systemic or topical.

Study Drug, Dosage, and Mode of Administration: INCB018424 cream is supplied in 3 dose strengths (1.5%, 0.5%, and 0.15%) and packaged as 15 g per tube.

On Day 1, the application regimen is to be determined by weighing a tube before and after the subject applies a thin film of study drug to the affected areas. For the determination of dosage, subjects should remove study drug from the tube in fingertip units until all of the areas to be treated are covered by a thin film. Subjects will be advised to limit use to no more than 1 tube per application.

Study drug will be applied topically as a thin film to the affected areas in the morning and in the evening at least 1 hour before bedtime.

If a subject has vitiligo present on more than 20% of BSA, the application of study drug will be limited to ≤ 20% of the subject's total BSA and areas treated at baseline should continue to receive treatment until the end of the double-blind period (Week 52) unless the subject meets criteria for stopping study drug because of an AE.

Reference Therapy, Dosage, and Mode of Administration: Vehicle cream is matching in appearance to INCB018424 cream and is to be applied in the same manner as INCB018424 cream.

Study Schedule/Procedures:

Study visits are as follows:

Screening: Up to 28 days before enrollment. Screening will begin at the time that the subject signs the informed consent and will continue until the date the subject is enrolled in the study (Day 1).

Vehicle-controlled, double-blind treatment: Subjects will have study visits on Day 1 and at Weeks 4, 8, 12, 18, and 24 for assessment of safety and efficacy.

Continued double-blind treatment: Subjects will have study visits at Weeks 28, 34, 40, 46, and 52 for assessment of safety and efficacy.

Open-label extension: Subjects will have visits at Weeks 56, 68, 80, 92, 104, 116, 128, 140, and 156 for assessment of safety and efficacy.

On the day of a visit, subjects should not apply the study drug at home and will apply the next dose of study drug from the new kit in the clinic. Subjects will be given a daily diary to record application times. Subjects will also be instructed to bring all study drug tubes with them to each visit so that compliance can be assessed.

Safety follow-up: Subjects will have follow-up assessments approximately 1, 3, and 6 months after the last dose of study drug to assess safety and efficacy. If prohibited treatment for vitiligo is started, then an earlier follow-up visit will be performed as a final, and thus end-of-study, visit.

Safety assessments:

At each scheduled study visit at the clinical site, targeted physical examinations, vital sign collection, laboratory assessments, collection of concomitant medications, and AE assessments will be performed.

Urinalysis and a 12-lead ECG will be performed at screening and end of treatment. All laboratory assessments will be performed using a central laboratory except for urine pregnancy tests. Toxicities will be monitored continuously and will be graded using the National Cancer Institute CTCAE v4.03 criteria.

Efficacy assessments:

The VASI (face and total body) and BSA (face and total body) will be conducted at every visit, and VETF will be conducted at every on-treatment visit through Week 104 (inclusive).

[redacted] Patient Global Impressions of Change-Vitiligo will be conducted on Day 1 and at Weeks 12, 24, 40, 52, 68, 80, 92, 104, 116, 128, 140, and 156 as well as the Month 6 follow-up visit.

[redacted]

Estimated Duration of Participation: Screening is up to 28 days (4 weeks), the double-blind, vehicle-controlled treatment period is 24 weeks, the continued double-blind treatment period is 28 weeks (52-week cumulative double-blind), the optional open-label extension is 104 weeks, and safety follow-up is 24 weeks. Total duration is up to 184 weeks.

Estimated Number of Subjects: Approximately 150 subjects in 5 dose groups of 30 subjects each.

Principal Coordinating Investigator: Dr. [redacted] Boston, MA

Statistical Methods: The sample size selection is based on the assumed response rates of 55% for the INCB018424 1.5% cream BID group and 5% for the vehicle group. Using a 2-sided Bonferroni corrected alpha of 0.025, 25 subjects per group will have a > 90% power to detect such a difference between either one of the active treatment groups and the vehicle group based on Fisher's exact test due to small expected frequency of responders in the vehicle group. Assuming a 20% drop-out rate during the first 24 weeks, approximately 150 subjects will need to be randomized. For the primary and key secondary analyses, comparisons between each active group and vehicle at Week 24 will be performed with a logistic regression. A graphical approach based on weighted Bonferroni will be used to control the familywise error rate (2-sided, 0.05) for all elementary hypotheses for primary and key secondary endpoints. All secondary [redacted] efficacy measures will be evaluated using descriptive statistics. The clinical safety data (vital signs, routine laboratory tests, and AEs) will be analyzed using descriptive statistics. [redacted]

An interim analysis to estimate treatment response and facilitate planning for future studies will be conducted when at least half of the randomized subjects reach Week 12 and again at Week 24.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or Term	Definition
AA	alopecia areata
AD	atopic dermatitis
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	total exposure
BID	twice daily
BSA	body surface area
CFR	Code of Federal Regulations
CL	clearance
CLA	cutaneous lymphocyte antigen
C_{max}	maximal plasma concentration
COMFORT	Controlled Myelofibrosis Study With Oral Janus-Associated Kinase Inhibitor Treatment
C_{ss}	plasma concentration at steady state
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
EOT	end of treatment
ET	early termination
F	percentage of systemic bioavailability
F-BSA	facial body surface area
FDA	Food and Drug Administration
fingertip unit	The amount of cream applied from the distal skin-crease of the tip of the index finger. The distal skin-crease is the skin-crease over the joint nearest the end of the finger.
F-PaGVA	facial assessment of the Patient's Global Vitiligo Assessment

Abbreviation or Term	Definition
F-PhGVA	facial assessment of the Physician's Global Vitiligo Assessment
FSH	follicle-stimulating hormone
F-VASI	facial assessment of the Vitiligo Area and Severity Index
FWER	familywise error rate
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
H	head/neck
HIPAA	Health Insurance Portability and Accountability Act of 1996
HLA-DR	human leukocyte antigen – antigen D related
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgM	immunoglobulin M
IL	interleukin
IL-2R	interleukin-2-receptor
IN	Investigator Notification
INF	interferon
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
JAK	Janus kinase
LL	lower limbs
MHC	major histocompatibility complex
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no-observed-adverse-effect level
PaGIC-V	Patient Global Impression of Change for Vitiligo
PaGVA	Patient's Global Vitiligo Assessment
palmar method of BSA assessment	1% BSA for each subject is approximately equal to the surface area of their palm plus 5 digits; handprint may be used interchangeably
PASI	Psoriasis Area Severity Index
PhGVA	Physician's Global Vitiligo Assessment

Abbreviation or Term	Definition
PK	pharmacokinetics
PV	polycythemia vera
QD	once daily
RNA	ribonucleic acid
SAE	serious adverse event
STAT	signal transducers and activators of transcription
SUSAR	Suspected Unexpected Serious Adverse Reactions
T	trunk
T-BSA	total body surface area
T-PaGVA	total body assessment of the Patient's Global Vitiligo Assessment
T-PhGVA	total body assessment of the Physician's Global Vitiligo Assessment
TEAE	treatment-emergent adverse events
TNF-α	tumor necrosis factor-alpha
TSH	thyroid-stimulating hormone
T-VASI	full body assessment of Vitiligo Area and Severity Index
UL	upper limbs
ULN	upper limit of normal
VASI	Vitiligo Area and Severity Index
VASI50	≥ 50% improvement from baseline in Vitiligo Area and Severity Index score
VASI75	≥ 75% improvement from baseline in Vitiligo Area and Severity Index score
VASI90	≥ 90% improvement from baseline in Vitiligo Area and Severity Index score
VETF	Vitiligo European Task Force
[redacted]	[redacted]

1. INTRODUCTION

INCB018424 cream is a topical formulation of INCB018424 phosphate (hereafter referred to as INCB018424) under development for the treatment of subjects with AA, AD, and vitiligo. INCB018424 is an inhibitor of the JAK family of protein tyrosine kinases. Mitogenic and inflammatory cytokines are strongly implicated in the pathogenesis of psoriasis, AA, AD, and vitiligo. [redacted]

1.1. Vitiligo

Vitiligo is an acquired depigmenting disorder that results from the disappearance of functioning melanocytes from the epidermis. Vitiligo is estimated to affect 0.5% to 1% of the population worldwide, causing disfigurement and decreased quality of life (Alikhan et al 2011). Vitiligo is characterized by well-circumscribed depigmented areas of the skin. Generalized vitiligo is the most common manifestation and often involves the face and acral regions. About half of patients are diagnosed before age 20 (Lotti et al 2008). The prevalence is similar between men and women, and there is no known difference in presentation according to skin type or race. Vitiligo is associated with autoimmune diseases such as Sutton nevus, thyroid disorders, juvenile diabetes mellitus, pernicious anemia, and Addison's disease. The natural course of the disease is generally unpredictable, but 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). Response to treatment varies, can be time intensive, slow to respond to treatment, and often produces disappointing results if repigmentation is cosmetically unacceptable.

Vitiligo can cause severe psychological distress and morbidity and decreased quality of life, particularly in darker skinned individuals, due to the large difference in skin tone between pigmented and unpigmented areas. Involvement of exposed skin, such as the face and hands, can have a major impact on self-esteem. In some societies, there is poor acceptance and understanding of the disease, to the extent of discrimination against affected individuals (Lotti et al 2008). Therefore, there is a need to identify new efficacious treatments for vitiligo.

1.2. Autoimmunity and Vitiligo

Vitiligo is believed to be a TH1-mediated process dependent on the production of IFN-γ to drive the response. CD8+ T cells are observed in sites of depigmentation, and evidence suggests they play an important role in melanocyte destruction in vitiligo (van den Boorn et al 2009). Immunohistochemical examination of inflammatory infiltrates in perilesional vitiligo skin using single and double immunostaining for melanocytes, Langerhans cells, T cells, and macrophages demonstrated that T cells from these infiltrates had dramatic production of IL-2R and increased CD8:CD4 ratio. Additionally, these investigations revealed higher densities of melanocytes in normal skin versus nonaffected skin in subjects with vitiligo. Thus, there is evidence that melanocyte destruction may be cytotoxic CD8 T-cell mediated (Mohammed et al 2015). In perilesional vitiligo skin, infiltrating T cells express activation molecules, such as IL2R-CD25,

HLA-DR, and MHC II and the CLA typical of skin homing. They also produce cytokines such as INF-γ and TNF-α. Through these mechanisms infiltrating T cells kill melanocytes within the skin, thereby causing the loss of pigmentation characteristic for nonsegmental vitiligo (Guerra et al 2010).

Le Poole et al (1996) studied the perilesional skin of patients suffering from inflammatory vitiligo (a rare subtype of vitiligo). In these patients, the perilesional skin is red, itchy, and irritated, and the inflammation progresses toward skin with remaining melanocytes. The researchers found that melanocyte densities were 2.5 times greater in control skin than in the pigmented nonlesional skin of patients and that in perilesional skin, there was a marked decrease in density even when compared with nonlesional skin. CD3 staining of T cells was significantly greater in perilesional skin when compared with nonlesional or lesional skin. Notably, in perilesional skin, T-cell infiltrates were substantially increased in the epidermal compartment and were mostly concentrated where melanocyte destruction occurs (at the epidermal basal layer). Overall, it was determined that epidermis-infiltrating T cells demonstrate an increased CD8/CD4 ratio and increased IL-2 receptor expression. Perilesional skin biopsies of inflammatory vitiligo had a decreased CD4/CD8 T-cell ratio. This suggests that the destruction of melanocytes could be cytotoxic CD8 T-cell mediated. All of the patients also exhibited perilesional HLA-DR expression (MHC class II receptor), particularly along basal and suprabasal keratinocytes, and the authors argued that this finding could be associated with local T-cell reactivity. From an autoimmune perspective, their results suggest that a melanocyte-specific immune reaction, involving most notably T cells, among other immune mediators, is likely involved in the pathogenesis of vitiligo (Le Poole et al 1996).

Grimes et al (2004) investigated the potential role of cytokines in a clinical study in which vitiligo patients were treated with 0.1% tacrolimus ointment, an immunomodulatory drug thought to inhibit T-cell activation and consequently diminish the production and secretion of proinflammatory cytokines. Punch biopsies were performed at baseline from depigmented, non-sun-exposed lesional skin and adjacent nonlesional skin, and similar biopsies were taken from non–sun-exposed control skin. Following the 24-week treatment period, repeat biopsies were excised. Some level of repigmentation occurred in 89% of patients, most of which significantly occurred in the face and neck regions. In terms of cytokine expression, patient involved and uninvolved skin at baseline demonstrated significantly increased expression of IL-10, IFN-c, and TNF-α when compared with expression in control skin. Post-treatment, the only significant difference was the decreased expression of TNF-α in both lesional and nonlesional skin of the vitiligo patients. These findings suggest that a cytokine imbalance is likely involved in the pathogenesis of vitiligo and that the apparent suppression of TNF-α by tacrolimus is a possible means of facilitating repigmentation. Also, it is important to note that repigmentation with tacrolimus was most noted in sun-exposed areas (ie, the face and neck). Thus, it could also be suggested that suppression of cytokines, namely TNF-α, somehow facilitates the UV stimulation of melanogenesis and, ultimately, the repopulation of melanocytes in vitiliginous skin. These results clearly indicate a plausible role for cytokines in the pathogenesis of vitiligo (Grimes et al 2004).

1.3. Role of JAKs in Vitiligo

There is limited knowledge of topical JAK inhibitors for treatment of vitiligo [redacted] Harris et al (2016) published a case report of a 35-year-old man with a 19-year history of concurrent AA and vitiligo who was treated with oral ruxolitinib 20 mg BID for 20 weeks who subsequently had hair regrowth as well as repigmentation of areas affected with vitiligo. Alopecia areata is an autoimmune condition that may coexist in patients with vitiligo and is also believed to be IFN-γ driven and dependent on CD8+ T cell activity. Craiglow and King (2015) reported the case of a woman, approximately 50 years old, with widespread and progressive vitiligo of 1 year duration who did not have a response to topical steroids, tacrolimus ointment, and narrowband UV-B phototherapy who was treated with oral tofacitinib at 5 mg QD (50% of the approved dose for rheumatoid arthritis) and who had repigmentation after 5 months of treatment. [redacted]

Based on these observations, an investigator-initiated study was conducted using open-label INCB018424 cream BID in 12 patients with vitiligo who had a minimum of 1% BSA affected. The primary endpoint was improvement from baseline in VASI at Week 20. The results showed a 76% improvement in F-VASI and 26% improvement in T-VASI, with 7 of 9 patients who completed the 20-week period demonstrating repigmentation (D. Rosmarin, MD, unpublished data, September 2016).

Due to the hematological liabilities associated with systemic JAK inhibition, topical JAK inhibitors are a promising approach to deliver JAK inhibition for T-cell–mediated disease localized to the epidermis such as vitiligo. The JAK1/2 inhibitor INCB018424 has been used systemically in myeloproliferative disorders, and a topical formulation of INCB018424 cream has been developed and demonstrated preliminary evidence of activity in subjects with psoriasis, AA (DuBois et al 2016), and vitiligo.

[redacted]

1.6. Clinical Experience

1.6.1. Clinical Efficacy With Topical INCB018424 Cream in Vitiligo

An investigator-initiated, 20-week, open-label POC study with extension up to 52 weeks of INCB018424 cream 1.5% BID is currently ongoing. The primary outcome of the study is improvement in VASI from baseline to Week 20. Eleven patients with vitiligo with a minimum of 1% affected BSA were enrolled into the study. At Week 20, 76% improvement in facial VASI score was observed in patients with significant facial vitiligo, and 26% improvement in overall VASI from baseline to Week 20 was also observed. These changes were considered to be a clinically meaningful response. Slower response was observed in acral areas as compared with facial areas. Reported AEs considered related to drug were mild and included erythema, hyperpigmentation in skin where drug was applied, and transient acne. Overall, INCB018424

cream was well-tolerated. The hyperpigmentation was observed in areas with subsequent repigmentation and may be predictive of response to study drug.

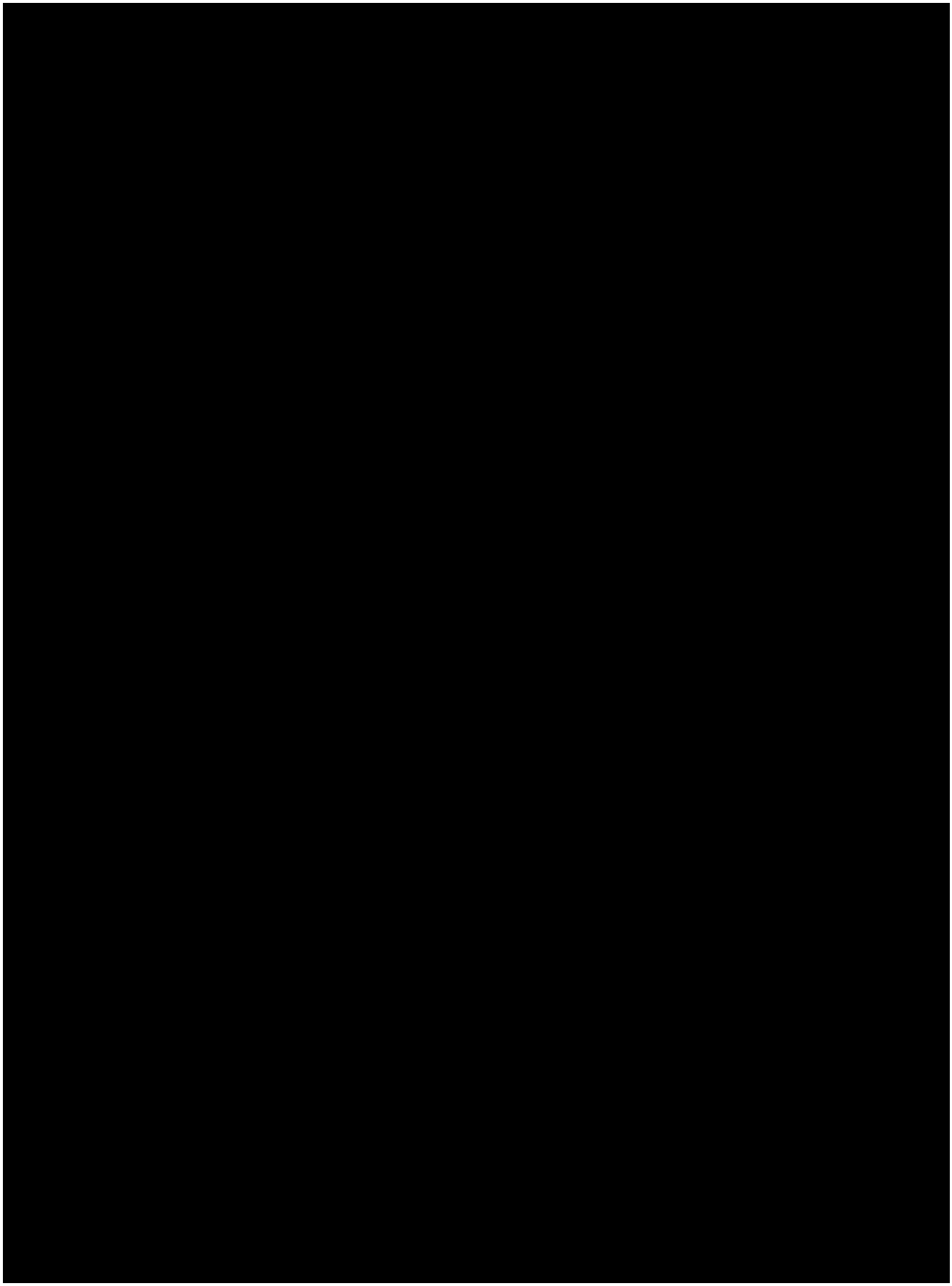
1.6.2. Clinical Efficacy With Topical INCB018424 Cream in Psoriasis

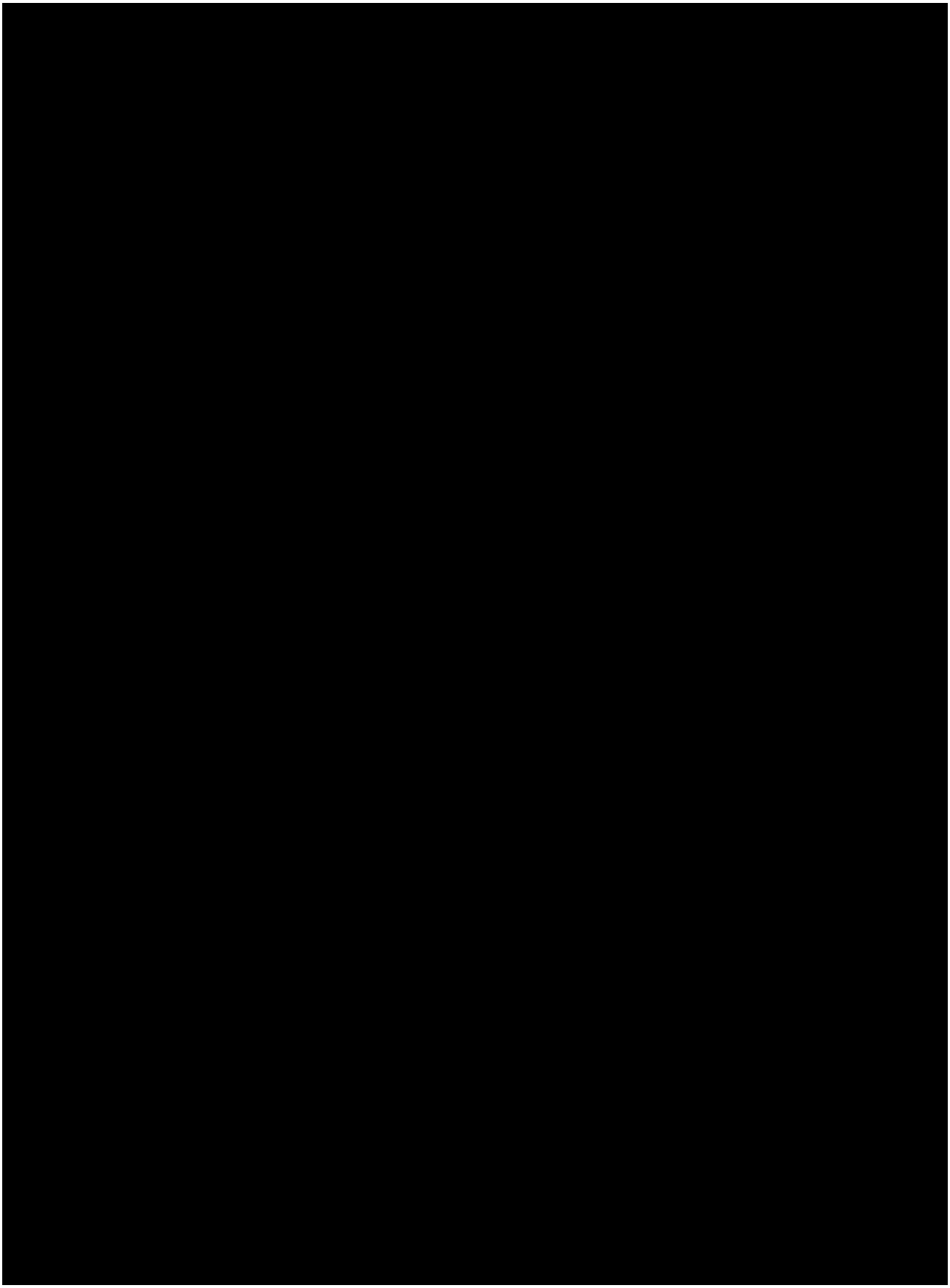
In a double-blind, vehicle- or comparator-controlled, ascending dose, safety, tolerability, PK, and preliminary efficacy study of INCB018424 cream in subjects with plaque psoriasis (Study INCB 18424-201), efficacy was demonstrated with both the 1% cream applied QD and the 1.5% cream applied BID with a trend toward a dose response. Improvement in lesion thickness, erythema, scaling, and reduction in total lesion area were observed in comparison to the vehicle. Reductions in mean lesion scores were 53% for 1% cream QD versus 32% for vehicle ($p \leq 0.05$); 54% for 1.5% cream BID versus 27% for vehicle ($p \leq 0.05$); 46% for 1.5% cream BID versus 40% for Dovonex® cream; and 58% for 1.5% cream BID versus 44% for Diprolene AF® cream.

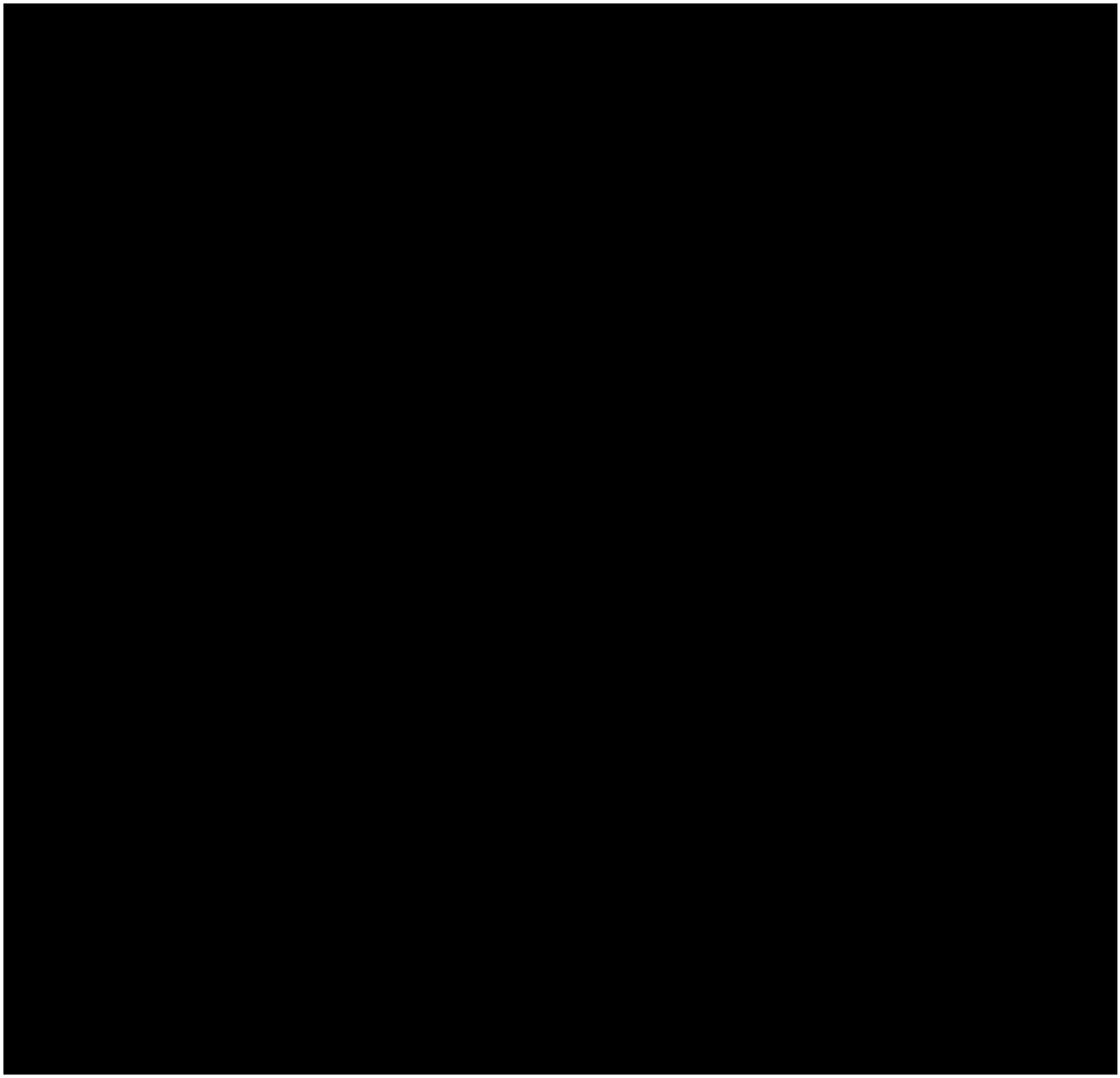
[redacted]

Study INCB 18424-203 was a 12-week, randomized, multicenter, parallel-group, vehicle-controlled, double-blind, dose-ranging study designed to evaluate the safety and efficacy of QD application of INCB018424 cream (0.5%, 1.0%, or 1.5%) relative to vehicle cream in subjects with stable plaque psoriasis. Within each active treatment group, the mean scores for the individual and total psoriasis lesion assessments, the PASI, the Physician's Global Assessment, and the mean treatable percent BSA decreased from baseline to each subsequent assessment, which indicated an overall lessening of disease severity. Thus, the efficacy analyses collectively revealed that all 3 doses of INCB018424 cream, when applied topically QD for 12 weeks, were effective in decreasing the individual signs of lesion severity, lesion area, and the overall disease severity of psoriatic plaques.

[redacted]







1.6.5. Oral INCB018424 (Ruxolitinib) Safety

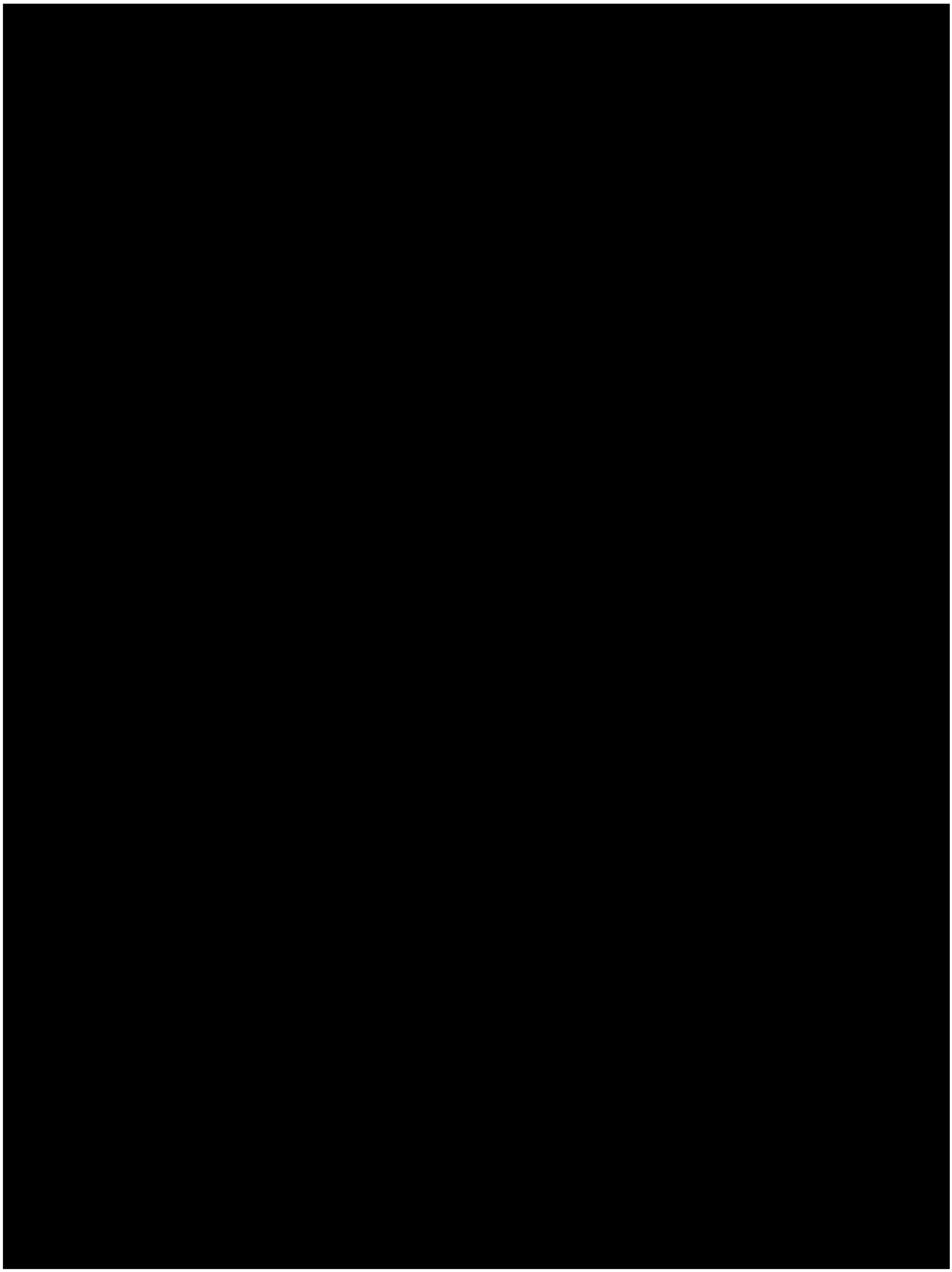
In the randomized period of the 2 pivotal studies in myelofibrosis, COMFORT-I and COMFORT-II, discontinuation because of AEs regardless of causality was observed in 11.3% of subjects. The most frequently reported adverse drug reactions were thrombocytopenia and anemia. Hematological adverse reactions (any CTCAE grade) included anemia (82.4%), thrombocytopenia (69.8%), and neutropenia (16.6%). Anemia, thrombocytopenia, and neutropenia are dose-related effects. The 3 most frequent nonhematological adverse reactions were bruising (21.6%), dizziness (15.3%), and headache (14.0%). The 3 most frequent nonhematological laboratory abnormalities were increased alanine ALT (27.2%), increased AST (18.6%), and hypercholesterolemia (16.9%).

Long-term follow-up in subjects with myelofibrosis (including 615 subjects treated with ruxolitinib during the controlled and extension phases of Studies INCB 18424-251 cutoff 01 OCT 2012; COMFORT-I: 02 SEP 2012; and COMFORT-II: 01 SEP 2012) has shown that, as expected, the numbers and proportions of AEs and SAEs has increased; however, no new safety signals have emerged (median duration of exposure for this population is 27.6 months, with 1345.78 patient-years of exposure).

In Study INCB 18424-258, in subjects with myelofibrosis with a platelet count between 50 and 100×10^9/L, beginning treatment with 5 mg BID was well-tolerated, avoided levels of thrombocytopenia associated with a high risk of significant bleeding, and provided an opportunity to increase the dose of ruxolitinib in a safe manner.

Overall, the safety profile of ruxolitinib in the PV population is generally consistent with that observed in the myelofibrosis population. Ruxolitinib was generally well-tolerated in subjects with PV, and only a small proportion of subjects discontinued ruxolitinib because of AEs (3.6%). Most of the AEs were managed by dose modifications. Hematological toxicities were less frequent and less severe in subjects with PV as compared with those observed in subjects with myelofibrosis. No new safety signals emerged from a study in pancreatic cancer in combination with capecitabine. The AE profile of ruxolitinib was also assessed in 198 healthy subjects, subjects with various degrees of renal (n = 32) or hepatic (n = 24) impairment, and subjects with RA (n = 59). Adverse events were, in general, mild and resolved without interventions.

A thorough QT study was conducted in 50 healthy subjects. There was no indication of a QT/QTc-prolonging effect of ruxolitinib in single doses up to a supratherapeutic dose of 200 mg, indicating that ruxolitinib has no effect on cardiac repolarization.



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2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

- To establish the efficacy of 24 weeks of treatment with INCB018424 cream in subjects with vitiligo.

2.1.2. Secondary Objectives

- To estimate the dose-response relationship of INCB018424 cream at Weeks 24 and 52.
- To evaluate the safety and tolerability of INCB018424 cream in subjects with vitiligo.

[redacted]

2.2. Study Endpoints

2.2.1. Primary Endpoint

- Proportion of subjects treated with INCB018424 cream who achieve a ≥ 50% improvement from baseline in F-VASI score (F-VASI50) at Week 24 compared with subjects treated with vehicle.

2.2.2. Secondary Endpoints

2.2.2.1. Key Secondary Endpoints

- Proportion of subjects who achieve an F-PhGVA of clear or almost clear at Week 24.
- Proportion of subjects who achieve a ≥ 50% improvement from baseline in T-VASI at Week 52.

2.2.2.2. Other Secondary Endpoints

- Assessment of the dose response on percentage change from baseline in F-VASI during the treatment periods.
- Mean and percentage change from baseline in F-VASI score during the treatment periods.

- Proportion of subjects who achieve an F-VASI50 during the treatment periods.
- Percentage change from baseline in F-BSA repigmentation during the treatment periods.
- Percentage change from baseline in T-BSA repigmentation during the treatment periods.
- Mean and percentage change from baseline in T-VASI score during the treatment periods.
- Mean and percentage change from baseline in VETF during the treatment periods.
- Proportion of subjects in each F-PhGVA and T-PhGVA category during the treatment periods.
- Proportion of subjects in each F-PaGVA and T-PaGVA category during the treatment periods.
- Proportions of subjects in each PaGIC-V category during the treatment periods.
- Proportion of subjects who report PaGIC-V of very much improved or much improved during the treatment periods.
- Times to achieve an F-VASI50 and T-VASI50.
- Times to achieve an F-PhGVA and T-PhGVA of clear or almost clear.
- Time to achieve a PaGIC-V of very much improved or much improved.
- Safety and tolerability assessed by monitoring the frequency, duration, and severity of AEs, physical examination, vital signs, and laboratory data for hematology, serum chemistry, and urinalysis.

[redacted]

3. SUBJECT ELIGIBILITY

Deviations from eligibility criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or subject safety. Therefore, adherence to the criteria as specified in the Protocol is essential.

3.1. Subject Inclusion Criteria

A subject who meets all of the following criteria may be included in the study:

1. Male and female subjects aged 18 to 75 years, inclusive.
2. Subjects with a clinical diagnosis of vitiligo.
3. Subjects with vitiligo with depigmented areas including:
    a. at least 0.5% of the total BSA on the face (0.5% BSA is approximately equal to the area of the subject's palm [without digits]) AND
    b. at least 3% of the total BSA on nonfacial areas (3% BSA is approximately equal to the area of 3 of the subject's handprints [palm plus 5 digits]).
4. Subjects who agree to discontinue all agents used to treat vitiligo from screening through the final follow-up visit. Over-the-counter preparations deemed acceptable by the investigator and camouflage makeups are permitted.
5. If receiving concomitant medications for any reason, must be on a stable regimen and anticipate staying on a stable regimen.
6. Willingness to avoid pregnancy or fathering of children based on the following criteria:
    a. Woman of nonchildbearing potential (surgically sterile with a hysterectomy and/or bilateral oophorectomy OR postmenopausal, defined by last menstrual period > 12 months before screening and confirmed by FSH).
    b. Woman of childbearing potential who has a negative serum pregnancy test at screening and a negative urine pregnancy test before the first dose on Day 1 and who agrees to take appropriate precautions to avoid pregnancy from screening through safety follow-up. Permitted methods that are highly efficacious in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.
    c. Man who agrees to take appropriate precautions to avoid fathering children from screening through safety follow-up. Permitted methods that are highly efficacious in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.
7. Ability to comprehend and willingness to sign an ICF.

3.2. Subject Exclusion Criteria

A subject who meets any of the following criteria will be excluded from the study:

1. Conditions at baseline that would interfere with evaluation of vitiligo.
2. Subjects who are receiving any kind of phototherapy, including tanning beds.
3. Subjects with other dermatologic disease besides vitiligo whose presence or treatments could complicate the assessment of repigmentation.
4. Subjects who have used skin bleaching treatments for past treatment of vitiligo or other pigmented areas.
5. Subjects who have received any of the following treatments within the minimum specified timeframes.
    a. Use of any biologic, investigational, or experimental therapy or procedure for vitiligo within 12 weeks or 5 half-lives (whichever is longer) of screening. Investigational biologics should be discussed with the sponsor to determine if a longer period of discontinuation is required.
    b. Use of laser or light-based vitiligo treatments, including tanning beds, within 8 weeks of screening.
    c. Use of immunomodulating oral or systemic medications (eg, corticosteroids, methotrexate, cyclosporine) or topical treatments that may affect vitiligo (eg, corticosteroids, tacrolimus/pimecrolimus, retinoids) within 4 weeks of screening.
6. Use of any prior and concomitant therapy not listed above that may interfere with the objective of the study as per discretion of the investigator, including drugs that cause photosensitivity or skin pigmentation (eg, antibiotics such as tetracyclines, antifungals) within 8 weeks of screening.
7. Subjects with a clinically significant abnormal TSH or free T4 at screening as determined by the investigator.
8. Subjects with cytopenias at screening, defined as follows:
    a. Leukocytes $< 3 \times 10^9$/L (2.5×10^9/L for subjects who are African-American).
    b. Neutrophils < lower limit of normal.
    c. Lymphocytes $< 0.8 \times 10^9$/L.
    d. Hemoglobin < 10 g/dL.
    e. Platelets $< 100 \times 10^9$/L.
9. Subjects with severely impaired liver function (Child-Pugh Class C) or ALT or AST $\geq 1.5 \times$ ULN on repeated assessment.
10. Subjects with impaired renal function with estimated creatinine clearance less than 60 mL/min.
11. Positive serology test results for HIV, for hepatitis B surface antigen or core antibody, or for hepatitis C virus antibody with detectable RNA at screening.

12. Subjects taking potent systemic CYP3A4 inhibitors or fluconazole within 2 weeks or 5 half-lives, whichever is longer, before the baseline visit (topical agents with limited systemic availability are permitted, see Appendix B).
13. Subjects who have previously received JAK inhibitor therapy, systemic or topical (eg, ruxolitinib, tofacitinib, baricitinib, filgotinib, lestaurtinib, pacritinib).
14. Women who were pregnant during the 12 months before screening.
15. Women who are breastfeeding.
16. Current or recent history (< 30 days before screening and/or < 45 days before randomization) of a clinically meaningful bacterial, fungal, parasitic, or mycobacterial infection.
17. History of unstable ischemic heart disease (including percutaneous cardiac intervention, myocardial infarction, or anginal acceleration within the past 6 months) or uncontrolled hypertension (blood pressure > 150/90 mmHg on at least 2 subsequent readings).
18. 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 subject's ability to comply with the administration schedule and study assessments.
19. 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 protocol.
20. Use of any prohibited medications (see Section 5.6.3) within 14 days or 5 half-lives (whichever is longer) of the baseline visit.
21. Donation of blood within 6 weeks before screening or of plasma within 2 weeks before screening and unwillingness to forego further blood product donation during the study.
22. Receipt of blood products within 2 months before screening.
23. Subjects with a history of malignancy, except for the following adequately treated, nonmetastatic malignancies: basal cell skin cancer not involving areas with vitiligo, squamous cell carcinomas of the skin not involving areas with vitiligo, or *in situ* cervical cancer.
24. Subjects who anticipate receiving a live or live-attenuated vaccination from screening through the final follow-up visit.
25. Subjects with known allergy or reaction to any component of the study formulation.
26. Subjects who, in the opinion of the investigator, are unable or unlikely to comply with the administration schedule and study evaluations.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is a 3-part, randomized, double-blind, and vehicle-controlled study in subjects with vitiligo who have depigmented areas including at least 0.5% of the total BSA on the face and at least 3% of the total BSA on nonfacial areas as determined by the palmar or handprint (palm plus 5 digits) method. Approximately 150 subjects, aged 18 to 75 years, will be randomized to 1 of 4 dose strengths of INCB018424 cream (1.5% BID, 1.5% QD, 0.5% QD, 0.15% QD) or vehicle in a 1:1:1:1:1 ratio and stratified by age (≤ 30 or > 30 years).

Subjects will receive blinded treatment for up to 52 weeks to examine efficacy, safety, and tolerability. The 3 parts of the study include a 24-week, double-blind, vehicle-controlled treatment period; a 28-week, continued, double-blind treatment period; and a 104-week, open-label extension period (see Figure 1). The primary endpoint of F-VASI50 will be evaluated at Week 24. After completion of the Week 24 assessments, subjects randomized to vehicle will be randomized to 1 of the 3 higher active treatment groups in a 1:1:1 ratio while maintaining the blind. Subjects in the 0.15% QD dose group who do not achieve a ≥ 25% improvement from baseline on F-VASI (nonresponders of F-VASI25) will be re-randomized to 1 of the 3 higher active treatment groups while maintaining the blind. Subjects randomized to INCB018424 0.15% QD who achieve a ≥ 25% improvement from baseline on F-VASI will remain on the same dose until Week 52. Subjects randomized to INCB018424 1.5% BID, 1.5% QD, and 0.5% QD will remain on the same dose until Week 52.

At any time during the study, if a subject has expansion of existing areas of depigmentation or development of new areas of depigmentation, then after a visit to document the VASI score and other measures of vitiligo, subjects are to apply study drug to those areas that are new or expanded since baseline in addition to areas treated since baseline as long as the total BSA to be treated does not exceed 20%. This visit may be unscheduled.

After completion of the Week 52 assessments, subjects who continue to be eligible for the study will be offered the opportunity to receive an additional 104 weeks of open-label treatment with INCB018424 1.5% cream BID. To be eligible, subjects must have completed the baseline, Week 24, and Week 52 visit assessments, be compliant with study medication, have no clinically significant changes in laboratory parameters from baseline (must meet entry criteria regarding cytopenias and liver assessments) and, in the opinion of the investigator, have no safety concerns regarding the previous 52 weeks of treatment with INCB018424 cream. In the open-label extension, subjects may be offered low-dose narrow band-UVB phototherapy in addition to INCB018424 cream in consultation with the investigator and sponsor.

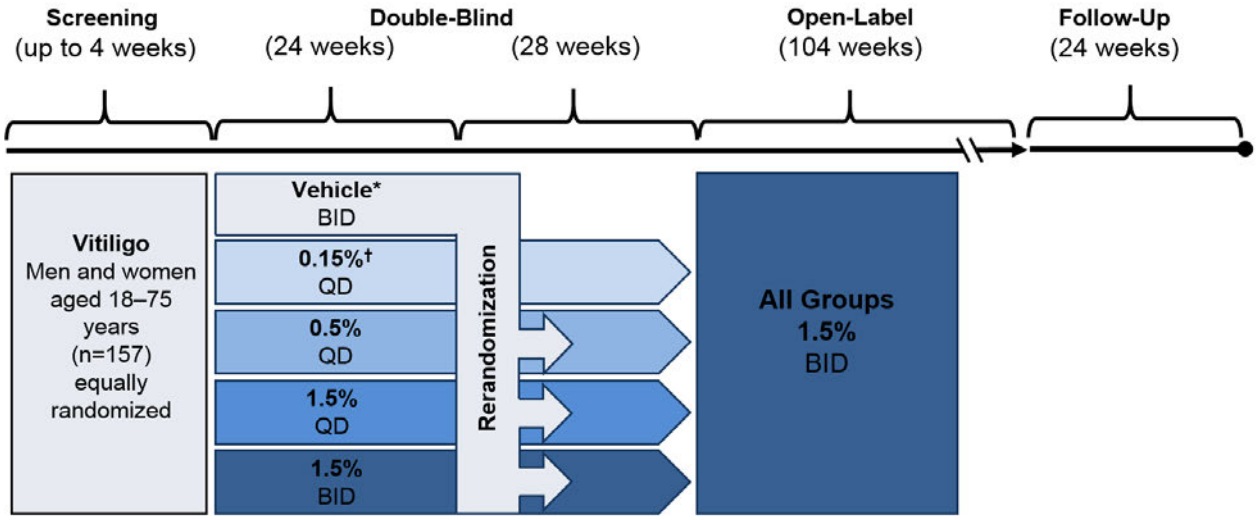
Subjects who are eligible for the open-label extension who have complete facial repigmentation (F-PhGVA score of 0) may stop applying study drug to the face, decrease the application rate to QD, or continue BID based on investigator judgement at Weeks 52 and 80 (after Week 80, subjects may also be permitted to modify their treatment regimen after the investigator has consulted with the sponsor). Subjects may continue to apply INCB018424 1.5% QD or BID to areas of vitiligo on the body; dose will be determined by the investigator based on level of repigmentation. A subject who had decreased the dose to QD or stopped applying INCB018424

to the face who has a loss of pigmentation on the face (F-PhGVA of at least 1) may increase the dose from QD to BID or restart application of INCB018424 1.5% BID after a visit to document the F-VASI score and other measures of vitiligo.

Sites will remain blinded to study drug, but some personnel at Incyte without direct contact with sites will be unblinded for the interim analyses. This internal committee will be charged with evaluating the unblinded interim analysis results (when at least 50% subjects first have Week 12 and then Week 24 data available). As full repigmentation is anticipated to be a slow process, the interim analysis results will determine preliminary efficacy of the treatment groups for future study and planning. After Week 24, the members of the primary endpoint assessment team from Incyte will be unblinded.

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

Figure 1: Study Design Schema



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

BID = twice daily; F-VASI = facial Vitiligo Area Scoring Index; QD = once daily.

4.2. Measures Taken To Avoid Bias

This is a randomized, placebo-controlled study with a 52-week double-blind period. Subjects will be randomized to 1 of 5 dose groups at baseline. After completion of the Week 24 assessments, subjects randomized to vehicle will be randomized to 1 of the 3 higher active treatment groups while maintaining the blind. Subjects in the 0.15% QD dose group who do not achieve a ≥ 25% improvement from baseline on F-VASI (nonresponders of F VASI25) will be re-randomized to 1 of the 3 higher active treatment groups while maintaining the blind. Subjects randomized to INCB018424 0.15% QD who achieve a ≥ 25% improvement from baseline on F-VASI will remain on the same dose until Week 52. Subjects randomized to INCB018424 1.5% BID, 1.5% QD, and 0.5% QD will remain on the same dose until Week 52.

4.3. Number of Subjects

The study will enroll approximately 150 subjects randomized equally to 1 of 5 treatment groups.

4.4. Duration of Treatment and Subject Participation

Screening is up to 28 days (4 weeks), the double-blind, vehicle-controlled, treatment period is 24 weeks, the continued double-blind treatment period is 28 weeks (52 weeks cumulative double-blind), the optional open-label extension treatment is 104 weeks, and safety follow-up is 24 weeks. Total duration is up to 184 weeks.

4.5. Overall Study Duration

The study begins when the first subject signs the ICF. The end of the study will occur when all subjects have discontinued study drug and have completed applicable follow-up assessments.

4.6. Study Termination

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

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

5. TREATMENT

5.1. Treatment Assignment

5.1.1. Subject Numbering and Treatment Assignment

The study will use an IRT for management of study enrollment. The system will assign the subject study number, track subject visits, randomize according to the defined parameters, maintain the blinding, and manage of study drug inventory.

5.1.2. Randomization and Blinding

For subjects who have met all study entry criteria and none of the exclusion criteria, the IRT should be contacted at baseline to obtain the study drug assignment. The system will assign the subject study number, track subject visits, randomize according to the defined parameters, and maintain the blind. The system will employ a configurable stratification algorithm with limits set to subject age (≤ 30 and > 30 years). Subjects will be randomized to 1 of 4 dose strengths of INCB018424 cream (1.5% BID, 1.5% QD, 0.5% QD, 0.15% QD) or vehicle in a 1:1:1:1:1 ratio. If any of the limits are reached, then the IRT will stop assigning randomization numbers to that group, and no additional subjects will be enrolled in that group. Subjects, investigators, and the sponsor (with the exception of members of the interim analysis and primary endpoint analysis assessment teams) will remain blinded to each subject's treatment assignment throughout the

study. Emergency unblinding will occur if an AE requires the investigator to be made aware of the subject's treatment assignment (see emergency unblinding procedures in Section 8.4 and refer to the Study Reference Manual).

5.2. INCB018424 Cream or Matching Vehicle

5.2.1. Description and Administration

INCB018424 cream or matching vehicle will be applied as a thin film BID, with applications at least 8 hours apart. The dose strengths for INCB018424 cream are 1.5%, 0.5%, and 0.15% (w/w free base equivalent) in a cream formulation along with the matching vehicle cream formulation containing only the vehicle.

Study drug will be applied in the clinic on the day of a study visit. The application regimen is to be determined by weighing a tube before and after the subject applies a thin film of study drug to the affected areas. For the determination of dosage, subjects should remove study drug from the tube in fingertip units until all of the areas to be treated are covered by a thin film. On the day of a visit, subjects should not apply the study drug at home and will apply the morning dose of study drug from the new kit in the clinic. If a subject has vitiligo present on more than 20% of BSA, the application of study drug will be limited to ≤ 20% of the subject's total BSA. Subjects will be advised to limit use to no more than 1 tube per application. Application instructions will be provided at study visits and via a diary card given to the subjects.

At each visit, an estimate of the percent BSA to be treated will be used by the IRT system to calculate the number of tubes of study drug to be dispensed. All areas identified at baseline should continue to be treated through the end of the double-blind period (Week 52) unless the subject meets criteria for stopping study drug because of an AE. If there are new areas to be treated, including expansion of existing areas or development of new areas, study drug should be applied to these areas in addition to the areas treated at baseline (up to 20% BSA), and the percentage of BSA to be treated will be recalculated and increased. This new estimate will be entered into the IRT system to calculate the number of tubes of study drug to be dispensed.

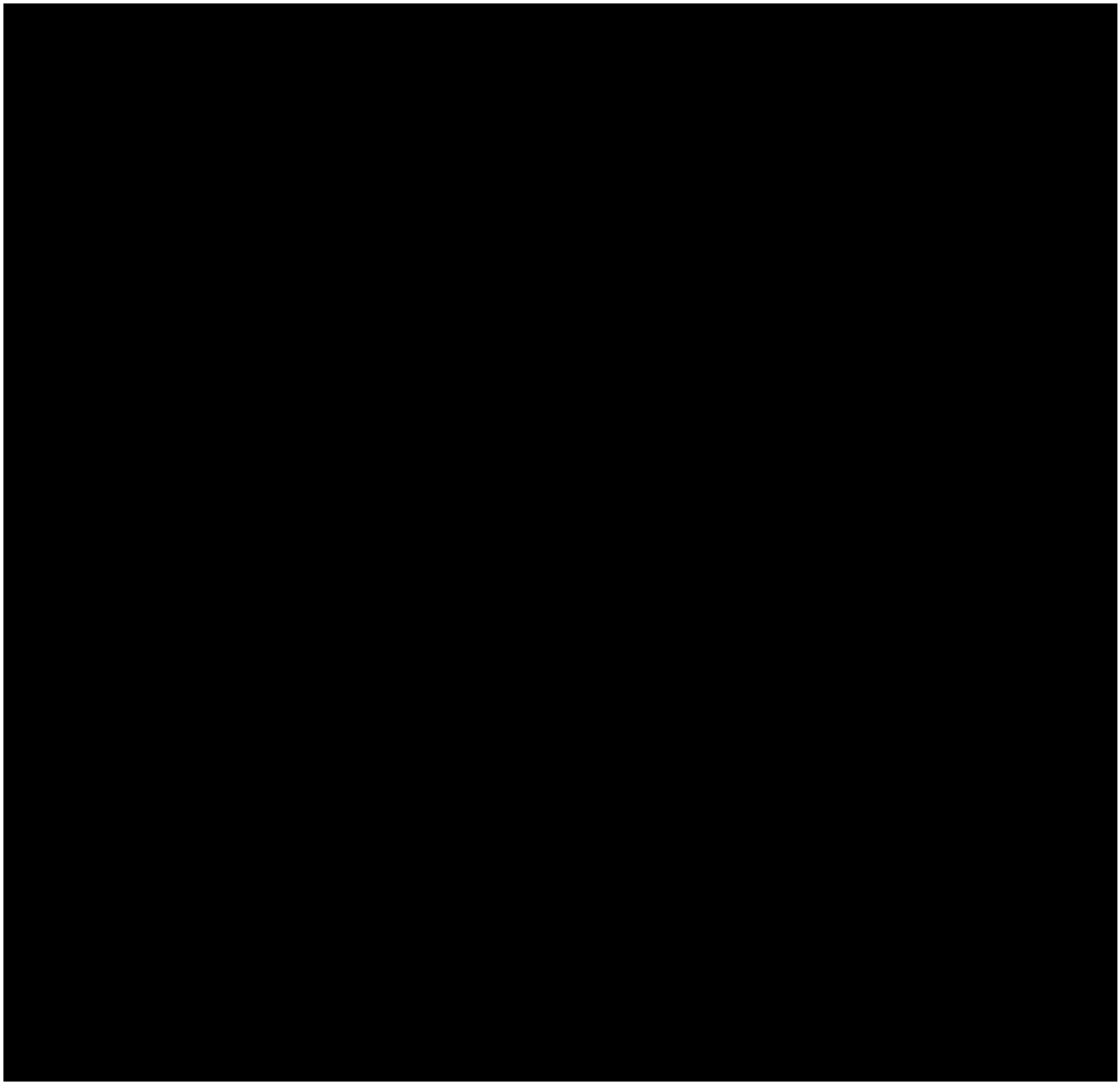
5.2.2. Supply, Packaging, and Labeling

INCB018424 drug product will be provided as INCB018424 cream 1.5% (w/w free base equivalent), INCB018424 cream 0.5%, INCB018424 cream 0.15%, or vehicle packaged as 15 g per tube. Tubes will include labeling for morning or for evening application.

All Incyte investigational product labels will be in the local language and will comply with the legal requirements of each participating country.

5.2.3. Storage

The INCB018424 drug product and vehicle cream should be stored at room temperature between 15°C and 30°C (59°F and 86°F).



5.3. Treatment Compliance

Compliance will be assessed by the site by reviewing the subject diaries and by weighing the study drug tubes. Subjects will also be questioned regarding study drug application technique, missed doses, and use of any additional topical or systemic prescriptions of other products or over-the-counter products. Starting at the Day 1 visit and each visit thereafter, a diary will be given to each subject in order to record the use of the study drug. The completed diary will be collected during each visit. Qualified clinical staff will review the subjects' entries for compliance. Subjects who are noncompliant with study drug (defined as nonuse of study drug BID as determined by the diary and < 70% or > 130% compliant based on expected application regimen and weight of study drug tubes) will have their administration instructions reinforced by the investigator or a qualified designee. Subjects 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 phase of the study. Subjects who are noncompliant on more than 1 occasion will be reinstructed by the investigator or a qualified designee, and the sponsor should be consulted by the investigator for instruction on the proper handling of the subject. Refer to the Study Reference Manual for additional compliance assessment details.

5.4. Treatment Interruptions and Adjustments

5.4.1. Dose Modifications

During the study, if the subject develops new areas of vitiligo or has an expansion of existing areas of vitiligo, subjects are permitted to apply study drug to the additional areas after a visit to document the F-VASI score and other measures of vitiligo (may be unscheduled visit), as long as the total treated areas do not exceed 20% BSA.

Subjects who are eligible for the open-label extension who have complete facial repigmentation (F-PhGVA score of clear) may stop applying study drug to the face, decrease the application rate to QD, or continue BID, based on investigator judgement, at Weeks 52 and 80. Subjects who have complete facial repigmentation that is first observed after Week 80 may also be permitted to modify their treatment regimen after the investigator has consulted with the sponsor about potentially modifying the subject's treatment regimen. Subjects may continue to apply INCB018424 1.5% QD or BID to areas of vitiligo on the body; dose will be determined by the investigator based on level of repigmentation. A subject who had decreased the dose to QD or stopped applying INCB018424 cream to the face who has a loss of pigmentation on the face (F-PhGVA of at least 1) may increase the dose from QD to BID or restart application of INCB018424 1.5% BID after a visit to document the F-VASI score and other measures of vitiligo.

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

In some circumstances, it may be necessary to temporarily interrupt treatment as a result of AEs or laboratory abnormalities that may have an unclear relationship to study drug. Except in cases of emergency, it is recommended that the investigator consult with the sponsor medical monitor (or other representative of the sponsor) before temporarily interrupting study drug. Additionally, the investigator must obtain approval from the sponsor before restarting study drug that was temporarily interrupted because of an AE or laboratory abnormality.

Individual subjects may have administration interrupted at the discretion of the investigator, in consultation with the sponsor, for AEs or laboratory abnormalities until these have resolved. Subjects MUST have administration interrupted in the following situations.

- The subject develops a Grade 2 increase in ALT (> 3 × ULN) or AST (> 3 × ULN); a Grade 2 decrease in ANC (< 1.5×10^9/L) or platelets (< 75×10^9/L); or a Grade 3 decrease in absolute lymphocyte count (< 0.5×10^9/L). Laboratory abnormalities should be confirmed with repeat testing within 48 hours whenever possible and expedited delivery of the laboratory results requested.
- The subject develops a Grade 3 or higher laboratory abnormality, with the exceptions of lipase (in which case a Grade 4, > 5 × ULN, results in discontinuation of study medication) or any asymptomatic triglyceride, cholesterol, or amylase elevations.

Laboratory abnormalities should be confirmed with repeat testing within a medically indicated timeframe, based upon the investigator's judgment and in collaboration with the sponsor's medical monitor, and expedited delivery of the laboratory results should be requested.

- The subject had a Grade 3 or 4 drug-related AE as determined by the investigator.

5.4.3. Criteria for Permanent Discontinuation of Study Drug

Subjects who have administration interrupted based on above criteria will be followed until the parameters return to the normal range or to baseline values. Laboratory evaluations can be repeated as frequently as daily. A subject who has had their dose interrupted based on these criteria may resume administration with study drug at a later time if the subject no longer meets the criteria for interrupting the dose with the sponsor's approval in consultation with the investigator. Subjects who meet withdrawal criteria (see Section 5.5.1) during study drug interruption will be withdrawn from the study and may not resume administration.

5.4.4. Criteria and Procedures for Dose Increases of Study Drug

A subject who had decreased the dose to QD or stopped applying INCB018424 cream to the face at Weeks 52 or 80 (or after Week 80; see Section 5.4.1) who subsequently has a loss of pigmentation on the face (F-PhGVA of at least 1) may increase the dose from QD to BID or restart application of INCB018424 1.5% BID after a visit to document the F-VASI score and other measures of vitiligo.

5.5. Withdrawal of Subjects From Study Treatment

5.5.1. Withdrawal Criteria

Subjects **must** be withdrawn from study treatment for the following reasons:

- The subject becomes pregnant.
- Consent is withdrawn.
- Further participation would be injurious to the subject's health or well-being, in the investigator's medical judgment.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

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

- If, during the course of the study, a subject is found not to have met eligibility criteria, then the medical monitor, in collaboration with the investigator, will determine whether the subject should be withdrawn from the study.
- If a subject is noncompliant with study procedures or study drug administration in the investigator's opinion, then the sponsor should be consulted for instruction on handling the subject.

5.5.2. Withdrawal Procedures

In the event that the decision is made to permanently discontinue the study drug, the subject will be withdrawn from the study, and the EOT visit should be conducted. Reasonable efforts should be made to have the subject return for a follow-up visit. These visits are described in Section 6. The last date of the last dose of study drug and the reason for subject withdrawal will be recorded in the eCRF.

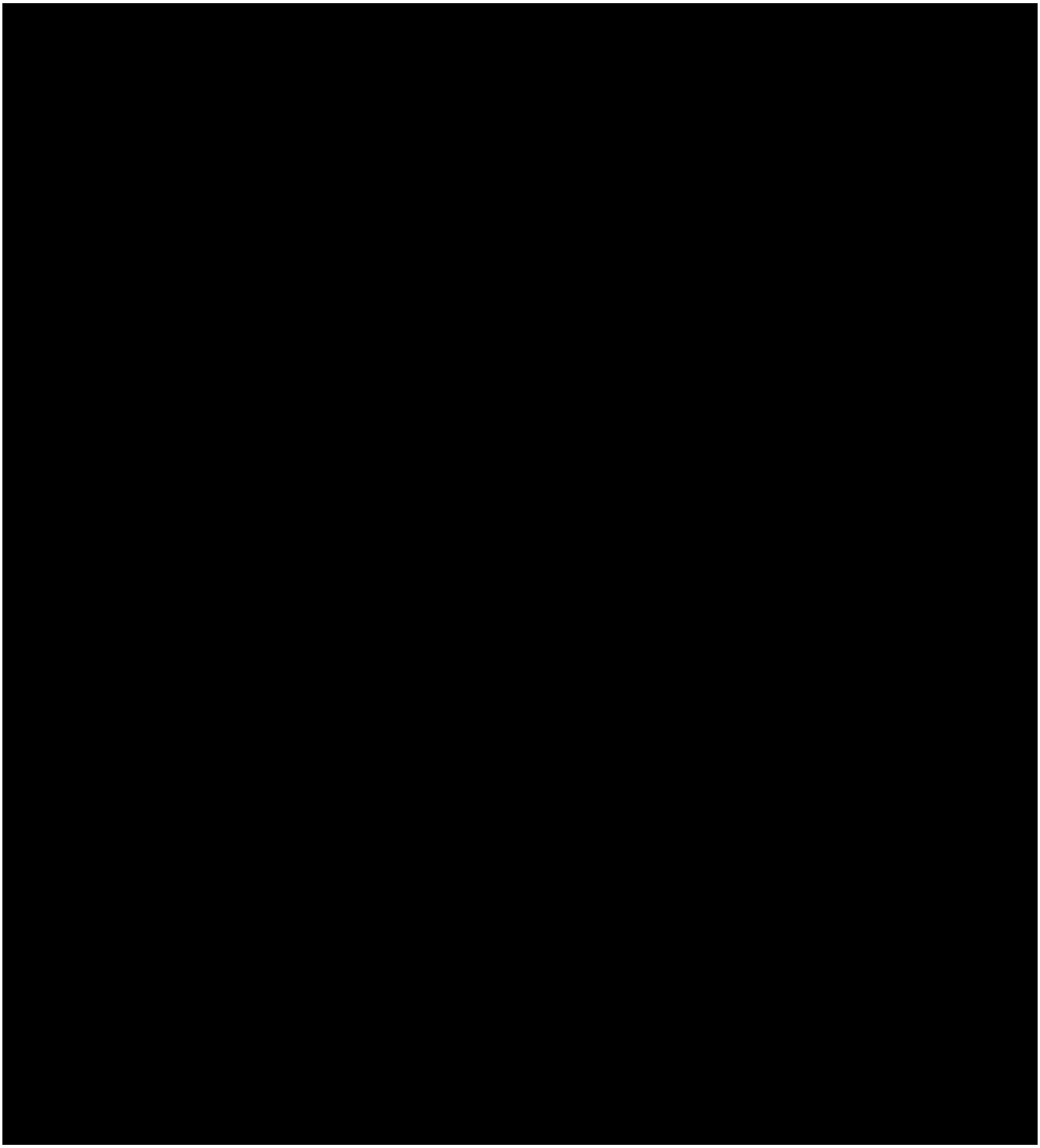
If a subject is withdrawn from the study:

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal must be documented in the subject's medical record and in the eCRF.
- The EOT visit should be performed.
- The date of the EOT visit should be recorded in the IRT.
- Subjects must be followed for safety until the time of the follow-up visit or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

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

5.6. Concomitant Medications

All concomitant medications and treatments must be recorded in the eCRF and ideally should remain stable through the end of the treatment portion of the study. All prior medications or treatments for vitiligo, all prior biologic medications, and any prior medications received up to 30 days before randomization will be recorded in the eCRF. Concomitant treatments and/or procedures that are required to manage a subject's medical condition during the study will also be recorded in the eCRF.



6. STUDY ASSESSMENTS

All study assessments will be performed as indicated in the schedule of assessments (Table 2, Table 3, and Table 4), and all laboratory assessments will be performed as indicated in Table 5.

Table 2: Schedule of Assessments During the Double-Blind, Vehicle-Controlled Treatment Period (Through Week 24)

Evaluation	Section	Screening	Double-Blind Treatment					
		Day -28 to -1	Day 1	Week 4 ± 3 d	Week 8 ± 3 d	Week 12 ± 3 d	Week 18 ± 7 d	Week 24 ± 7 d
Administrative procedures								
Informed consent	7.1	X						
Contact IRT	7.2	X	X	X	X	X	X	X
Inclusion/exclusion criteria	3	X	X					
Demography	7.3	X						
Medical history	7.3	X						
Prior/concomitant medications	7.4	X	X	X	X	X	X	X
Apply study drug	5.2		X	X	X	X	X	X
Study drug and diary card dispensed	7.10.1		X	X	X	X	X	X
Collect study drug tubes; collect and review diary cards	5.3			X	X	X	X	X
Assess compliance	5.3			X	X	X	X	X
Safety procedures/assessments								
Comprehensive physical examination[a]	7.5.2.1	X						X
Targeted physical examination	7.5.2.2		X	X	X	X	X	
Vital signs	7.5.3	X	X	X	X	X	X	X
Hematology and chemistry assessments	7.5.5	X	X	X	X	X	X	X
Serology and thyroid testing	7.5.5.5	X						
Urinalysis	7.5.5.3	X						
FSH[b]	7.5.5.4	X						
Pregnancy test[c]	7.5.5.4	X	X	X	X	X	X	X
12-lead ECG	7.5.4	X						
Assess AEs	7.5.1	X	X	X	X	X	X	X
Efficacy and other assessments								
VASI (face and total body)	7.6.1	X	X	X	X	X	X	X
BSA (face and total body)	7.6.2	X	X	X	X	X	X	X
VETF	7.6.3	X	X	X	X	X	X	X
[redacted]								
Physician – PhGVA (face and total body)	7.6.4		X			X		X
Patient – PaGVA (face and total body)	7.6.5		X			X		X
PaGIC-V	7.6.6					X		X

Table 2: Schedule of Assessments During the Double-Blind, Vehicle-Controlled Treatment Period (Through Week 24) (Continued)

Evaluation	Section	Screening	Double-Blind Treatment					
		Day -28 to -1	Day 1	Week 4 ± 3 d	Week 8 ± 3 d	Week 12 ± 3 d	Week 18 ± 7 d	Week 24 ± 7 d
[redacted]								

[a] Height and weight at screening only.
[b] Serum FSH to be performed for all postmenopausal women only (defined by last menstrual period > 12 months before screening and confirmation by FSH in the postmenopausal range).
[c] All women will have a serum pregnancy test conducted at the screening visit and urine pregnancy tests conducted at all other visits (including baseline).
[redacted]

Table 3: Schedule of Assessments During the Continued Double-Blind Period (Weeks 28 Through 52)

Evaluation	Section	Double-Blind Extension Period					Follow-Up	
		Week 28 ± 7 Days	Week 34 ± 7 Days	Week 40 ± 7 Days	Week 46 ± 7 Days	Week 52 EOT/ET ± 7 Days	Months 1 and 3 ± 7 Days	Month 6 EOS ± 7 Days
Administrative procedures								
Contact IRT	7.2	X	X	X	X	X	X	X
Prior/concomitant medications	7.4	X	X	X	X	X	X	X
Apply study drug	5.2	X	X	X	X			
Study drug and diary card dispensed	7.10.1	X	X	X	X			
Collect study drug tubes; collect and review diary cards	5.3	X	X	X	X	X		
Assess compliance	5.3	X	X	X	X	X		
Safety procedures/assessments								
Comprehensive physical examination	7.5.2.1					X		
Targeted physical examination	7.5.2.2	X	X	X	X		X	X
Vital signs	7.5.3	X	X	X	X	X	X	X
Hematology and chemistry assessments	7.5.5	X	X	X	X	X	X	X
Urinalysis[a]	7.5.5.3					X		
Pregnancy test[b]	7.5.5.4	X	X	X	X	X	X	X
12-lead ECG[a]	7.5.4					X		
Assess AEs	7.5.1	X	X	X	X	X	X	X
Efficacy and other assessments								
VASI (face and total body)	7.6.1	X	X	X	X	X	X	X
BSA (face and total body)	7.6.2	X	X	X	X	X	X	X
VETF	7.6.3	X	X	X	X	X		
[redacted]								
Physician - PhGVA (face and total body)	7.6.4			X		X		X
Patient - PaGVA (face and total body)	7.6.5			X		X		X
PaGIC-V	7.6.6			X		X		X
[redacted]								

[a] Urinalysis and 12-lead ECG to be conducted at the EOT visit (Week 52, Week 156, or early discontinuation).
[b] All women will have a urine pregnancy test conducted at all visits in this portion of the study.
[redacted]

Table 4: Schedule of Assessments for the Open-Label Extension Period (Weeks 52 Through 156)

Evaluation	Section	Open-Label Extension Period							Follow-Up	
		Week 52 ± 7 d	Week 56 ± 7 d	Week 68 ± 7 d	Week 80 ± 7 d	Weeks 92 and 104 ± 7 d	Weeks 116, 128, 140 ± 7 d	Week 156 ET/EOT ± 7 d	Months 1 and 3 ± 7 d	Month 6 EOS ± 7 d
Administrative procedures										
Contact IRT	7.2		X	X	X	X	X	X	X	X
Prior/concomitant medications	7.4		X	X	X	X	X	X	X	X
Apply study drug	5.2	X	X	X	X	X	X			
Study drug and diary card dispensed	7.10.1	X	X	X	X	X	X			
Collect study drug tubes; collect and review diary cards	5.3		X	X	X	X	X	X		
Assess compliance	5.3		X	X	X	X	X	X		
Safety procedures/assessments										
Comprehensive physical examination	7.5.2.1							X		
Targeted physical examination	7.5.2.2		X	X	X	X	X		X	X
Vital signs	7.5.3		X	X	X	X	X	X	X	X
Hematology and chemistry assessments	7.5.5		X	X	X	X	X	X	X	X
Urinalysis	7.5.5.3							X		
Pregnancy test[a]	7.5.5.4		X	X	X	X	X	X	X	X
12-lead ECG	7.5.4							X		
Assess AEs	7.5.1		X	X	X	X	X	X	X	X
Efficacy and other assessments										
VASI (face and total body)	7.6.1		X	X	X	X	X	X	X	X
BSA (face and total body)	7.6.2		X	X	X	X	X	X	X	X
VETF	7.6.3		X	X	X	X				
[redacted]										
Physician - PhGVA (face and total body)	7.6.4			X	X	X	X	X		X
Patient - PaGVA (face and total body)	7.6.5			X	X	X	X	X		X
PaGIC-V	7.6.6			X	X	X	X	X		X
[redacted]										

[a] All women will have a urine pregnancy test conducted at all visits in this portion of the study.

[redacted]

Table 5: Clinical Laboratory Assessments

Serum Chemistries[a]	Hematology
Albumin Alkaline phosphatase ALT AST Bicarbonate Blood urea nitrogen Calcium Chloride Creatinine Glucose Lactate dehydrogenase Phosphorus Potassium Sodium Total bilirubin Total serum protein	Hematocrit Hemoglobin Mean corpuscular volume Platelet count Red blood cell count Reticulocyte count White blood cell count White blood cell differential (5 part): • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils
Other	**Serology**
Urinalysis Urine pregnancy test (at site) Serum pregnancy test FSH Free T4 TSH	Hepatitis B surface antigen Hepatitis B core antibody Hepatitis B core IgM antibody Hepatitis C virus antibody HCV-RNA (only performed if antibody positive) HIV

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

6.1. Screening

Screening is the interval between the signing of the ICF and the day that the subject is randomized in the study. Informed consent must be obtained before performing any study-specific procedures. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during screening.

Results from the screening evaluations will be reviewed to confirm subject eligibility before randomization and administration of study drug. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the results to be in error. Additionally, a subject who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status (eg, following recovery from an infection).

6.2. Baseline

The results from the screening evaluations will be reviewed to determine whether the subject continues to meet the eligibility requirements as specified in the Protocol.

Subjects who have signed the ICF and meet all the entry criteria (see Section 3) may be randomized in the study.

6.3. Treatment

For subjects who are randomized and administered study drug on Day 1, the dates for subsequent study visits will be determined based on this day and should occur within the visit windows outlined in the schedule of assessments (Table 2, Table 3, and Table 4).

The treatment period begins when the subject receives their first dose of study drug on Day 1, which will be administered in the clinic. Tubes of INCB018424 cream or vehicle cream will be dispensed to subjects with detailed application instructions.

After completion of the Week 24 assessments in the double-blind, vehicle-controlled portion of the study, treatment assignment will not be unblinded. The members of the primary endpoint assessment team from Incyte will be unblinded, however.

Subjects randomized to vehicle will be randomized to 1 of the 3 higher active treatment groups while maintaining the blind. Subjects in the 0.15% QD dose group who do not achieve a ≥ 25% improvement from baseline on F-VASI (nonresponders of F-VASI25) will be re-randomized to 1 of the 3 higher active treatment groups while maintaining the blind. Subjects randomized to INCB018424 0.15% QD who achieve a ≥ 25% improvement from baseline on F-VASI will remain on the same dose until Week 52. Subjects randomized to INCB018424 1.5% BID, 1.5% QD, and 0.5% QD will remain on the same dose until Week 52.

Any increase or new areas of vitiligo may be treated, as long as the additional percent BSA is documented in the eCRF and the total BSA treated does not exceed 20%.

After completion of the Week 52 assessments, subjects who continue to be eligible for the study will be offered the opportunity to receive an additional 104 weeks of open-label treatment with INCB018424 1.5% cream BID.

If a decision is made that the subject will permanently discontinue study drug, then the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, then the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT page in the eCRF. The subject should be encouraged to return for the follow-up visits.

6.4. Follow-Up

Subjects will have follow-up assessments 1, 3, and 6 months after the last application of study drug. Although subjects will be asked not to apply any other medications for vitiligo during the follow-up period, if prohibited treatment for vitiligo is started, then an earlier follow-up visit may be performed. A final EOS visit should be performed, ideally no earlier than 30 days after the last dose of study drug. Adverse events and SAEs must be reported up until at least 30 days after the last dose of study drug, the date of the follow-up visit, or until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest. Reasonable efforts should be made to

have the subject return for the follow-up visits and report any AEs that may occur during this phase.

6.5. Unscheduled Visits

Unscheduled study visits may occur at any time medically warranted. Any assessments performed at those visits should be recorded in the eCRF. If there is worsening of vitiligo at an unscheduled visit, then an F-VASI score, T-VASI score, and [redacted] new areas of vitiligo, and then treatment of such areas may begin if the total affected treatment area is less than 20%.

6.6. Early Termination

In the event that any subject discontinues the study drug and subsequently the study before completion, regardless of reason, reasonable efforts should be made to have the subject return for an ET visit and have the EOT procedures completed as noted in Table 3 and Table 4.

Subjects who are noncompliant with study drug (defined as not documenting diary BID use and < 70% or > 130% compliant based on prescribed application regimen and weight of study drug tubes) will have the administration instructions reinforced by the investigator or a qualified designee. After reinforcement, subjects who again fail to meet 70% or 130% compliance benchmarks in a subsequent visit will be considered for withdrawal from the study. In such cases, the sponsor should be consulted by the investigator for instruction on the proper handling the subject before withdrawal.

7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

7.1. Administration of Informed Consent Form

Valid informed consent must be obtained from the study subject before conducting any study-specific procedures using an ICF approved by the local IRB/IEC that contains all elements required by ICH E6 and describes the nature, scope, and possible consequences of the study in a form understandable to the study subject. Local and institutional guidelines for ICF content and administration must be followed; the original signed ICF must be retained by the investigator, and a copy of the signed ICF must be provided to the study subject. The informed consent process for each subject must be documented in writing within the subject source documentation.

7.2. Interactive Response Technology Procedure

The IRT will be contacted to obtain a subject ID number when a subject enters screening. Upon determining that the subject is eligible for study entry, the IRT will be contacted to obtain the treatment assignment. Additionally, the IRT will be contacted at each regular study visit to update the study drug supply. See Section 5.1.1 for details on subject numbering and treatment assignment.

7.3. Demography and Medical History

7.3.1. Demographics and General Medical History

Demographic data and general medical history will be collected at screening.

7.3.2. Disease Characteristics and Treatment History

A disease-targeted medical and medication history will be collected at screening.

7.4. Prior and Concomitant Medications and Procedures

Prior and concomitant medications and procedures will be reviewed to determine subject eligibility. All concomitant medications and measures must be recorded in the eCRF, and any medication received or procedure performed within 30 days before randomization and up to the EOS will be recorded in the eCRF. The medication record will be maintained after signing the ICF to document concomitant medications, including any changes to the dose or regimen. Concomitant medications include any prescription, over-the-counter, or natural/herbal preparations taken or administered during the study period. Concomitant treatments and/or procedures that are required to manage a subject's medical condition during the study will also be recorded in the eCRF.

7.5. Safety Assessments

7.5.1. Adverse Events

Adverse events will be monitored from the time the subject signs the ICF. Subjects will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study. In order to avoid bias in eliciting AEs, subjects will be asked general, nonleading questions such as "How are you feeling?" All AEs (serious and nonserious) must be recorded on the source documents and eCRFs regardless of the assumption of a causal relationship with the study drug. The definition, reporting, and recording requirements for AEs are described in Section 8.

7.5.2. Physical Examinations

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

Clinically notable abnormalities that are considered clinically significant in the judgement of the investigator are to be reported as AEs.

7.5.2.1. Comprehensive Physical Examination

The comprehensive physical examination will include height and body weight (at screening) and assessment(s) 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; as well as a brief neurological examination.

7.5.2.2. Targeted Physical Examination

The targeted physical examination will be a symptom-directed evaluation. The targeted physical examination will include body weight and assessment(s) of the body systems or organs, as indicated by subject symptoms, AEs, or other findings.

7.5.3. Vital Signs

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

7.5.4. Electrocardiograms

All 12-lead ECGs will be performed with the subject in a recumbent or semirecumbent position after 5 minutes of rest.

Interpretation of the 12-lead ECG will be used to determine eligibility at screening. An additional ECG will be performed at the EOT visit (Week 52, Week 156, or if the subject discontinues treatment). Throughout the study, a 12-lead ECG may be conducted if associated with an AE or other signs or symptoms.

7.5.5. Laboratory Assessments

Clinical laboratory tests will be performed using a central laboratory, with the exception of urine pregnancy tests. A detailed description of the procedures for sampling, handling, storage, and shipment of the central laboratory samples and all material such as test tubes and labels is provided in the central Laboratory Manual. If unscheduled local laboratory tests are performed and those results lead to a dose modification, delay, or dose interruption, or if any additional non-Protocol–required test is performed because of an AE, then those results and the normal reference ranges for those analytes must be documented in the eCRF. Otherwise, unscheduled local laboratory test results do not need to be entered in the eCRF.

Tests required at each visit are shown in Table 2, Table 3, and Table 4. Additional analytes may be requested based on emerging data, if indicated for safety of study subjects. In addition, some subjects may receive additional assessments as medically indicated; results of nonrequired tests may also be entered in the eCRF.

7.5.5.1. Chemistry

A panel of standard serum chemistries will be analyzed at times shown in Table 2, Table 3, and Table 4. A list of required analytes is found in Table 5. All serum chemistries will be performed from blood samples collected without respect to food intake (ie, nonfasted).

7.5.5.2. Hematology

Hematology tests will be performed at each study visit indicated in Table 2, Table 3, and Table 4. A list of required analytes for scheduled visits is provided in Table 5.

7.5.5.3. Urinalysis

Urinalysis will be performed by a central laboratory at screening and EOT (Week 52, Week 156, or if the subject discontinues treatment, see Table 2, Table 3, and Table 4).

7.5.5.4. Pregnancy Testing

Pregnancy testing will be performed on all female subjects as noted in the schedules of assessments (Table 2, Table 3, and Table 4). Serum pregnancy test will be obtained at screening. A urine pregnancy test will be obtained all other visits. A positive urine pregnancy test should be confirmed by a serum pregnancy test.

7.5.5.5. Hepatitis and HIV Screening Tests

Hepatitis and HIV tests shown in Table 5 will be conducted during the screening period. If subjects are positive for active disease they should not be enrolled per exclusion criteria.

7.6. Efficacy Assessments

Efficacy assessments are conducted at the weeks noted in Table 2, Table 3, and Table 4.

7.6.1. Vitiligo Area and Severity Index

Areas affected by depigmentation due to vitiligo will be assessed using the VASI, which is a quantitative clinical tool that is analogous to the PASI used in psoriasis and is based on a composite estimate of the overall area of vitiligo patches at baseline and the degree of macular repigmentation within these patches over time.

In this study, F-VASI will be determined. F-VASI will be the percentage of depigmented vitiligo skin expressed as a percentage of BSA (hand unit) on the face and estimated by the investigator using the palmar or handprint (palm plus 5 digits) method. This will be an additional variable to be analyzed in addition to the vitiligo head/neck subscore.

[redacted]

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

$$VASI = \sum_{\text{all body sites}} [\text{hand units}] \; x \; [\text{Residual Depigmentation}]$$

Briefly, the body is divided into the following 6 separate and mutually exclusive sites: head/neck, hands, upper extremities (excluding hands), trunk, lower extremities (excluding feet), and feet. The percentage of vitiligo involvement is estimated in hand units by the same investigator during the entire course of the study. Hand unit is based on subject's hand size. Investigator uses his/her hand to mimic the subject's hand size to evaluate % BSA vitiligo involvement. The degree of depigmentation for each body site was determined and estimated to

the nearest of the following percentages: 0, 10%, 25%, 50%, 75%, 90%, or 100%. At 100% depigmentation, no pigment is present; at 90%, specks of pigment are present; at 75%, the depigmented area exceeds the pigmented area; at 50%, the depigmented and pigmented area are equal; at 25%, the pigmented area exceeds the depigmented area; at 10%, only specks of depigmentation are present. The VASI is then derived by multiplying the values assessed for the vitiligo involvement by the percentage of affected skin for each body site and summing the values of all body sites together (Hamzavi 2004, Dicle 2015). See Appendix C for full assessment tool.

7.6.2. Body Surface Area

At each visit, the BSA affected with vitiligo for each of 4 regions (head/neck [H], upper limbs [UL], trunk [T], and lower limbs [LL]) as a percent of the total BSA, as well as the face separately (depigmented area as a percent of the total area of the face) will be determined to the nearest 0.1% using, as guides, the palm plus 5 digits, with fingers tucked together and thumb tucked to the side (handprint), as 1% BSA and the thumb as 0.1% BSA.

If the subject has areas that exceed 20% that will not be treated with study drug, the BSA of these areas should be noted.

If worsening of vitiligo is present, then new areas, expansion of existing areas, or both are noted as present since the prior visit.

7.6.3. Vitiligo European Task Force Scale

The VETF proposed a system that combines analysis of extent, stage of disease (staging), and disease progression (spreading). Extent is evaluated using the rule of nines, already used in assessment of AD. Staging is based on cutaneous and hair pigmentation in vitiligo patches, and the disease is staged 0 to 4 on the largest macule in each body region, except hands and feet, which are assessed separately and globally as 1 unique area.

The staging scale is as follows:

- Stage 0: normal pigmentation (no depigmentation in area graded).
- Stage 1: incomplete pigmentation (including spotty depigmentation, trichrome, and homogeneous lighter pigmentation).
- Stage 2: complete depigmentation, a few white hairs do not change stage.
- Stage 3: partial hair whitening < 30%.
- Stage 4: complete hair whitening.

"Spreading" in VETF includes a dynamic dimension, since rapidly progressive vitiligo needs urgent intervention to stabilize the disease. The proposed grid allows scoring this dimension on a simple scale (+1: progressive; 0: stable; −1: regressive).

Spreading is assessed by combining Wood's lamp and electric light examinations in a dark room. Wood's lamp includes a magnifying lens to assess hairs, especially vellus hairs (Taïeb and Picardo 2007, Kawakami and Hashimoto 2011, Komen et al 2015).

See Appendix D for the full assessment tool.

7.6.4. Physician's Global Vitiligo Assessment

The severity of vitiligo will be assessed by the physician using the PhGVA, which has a 5-point scale (Table 6). Response will be reported for face and overall (F-PhGVA and T-PhGVA). Complete facial repigmentation is defined as an F-PhGVA of clear (0).

During the open-label extension, for subjects who have complete facial repigmentation at Week 52 or Week 80 or after Week 80, relapse is defined as increased areas of depigmentation, as determined by the investigator, by a change in F-PhGVA from 0 (clear) to 1 (almost clear) or from 0 (clear) to ≥ 2 (mild disease).

Table 6: Physician's Global Vitiligo Assessment Scale

Score	Severity	Description
0	Clear	No signs of vitiligo
1	Almost clear	Only specks of depigmentation present
2	Mild disease	Pigmented and depigmented areas are equal
3	Moderate disease	More or complete depigmentation (may include < 30% hair whitening)
4	Severe disease	Complete depigmentation plus > 30% hair whitening.

7.6.5. Patient's Global Vitiligo Assessment

The severity of vitiligo will be assessed by the subject using the PaGVA, which has a 5-point scale. Response will be reported for face and overall (F-PaGVA and T-PaGVA). The subject will be asked the following:

> How severe is your vitiligo on your face (or total body) with respect to the area covered by white skin?
>
> Responses: No white patches (No vitiligo); Mild; Moderate; Severe; Very Severe.

7.6.6. Patient Global Impression of Change-Vitiligo

The PaGIC-V is an assessment of improvement by the subject. It is a 7-point scale comparing the vitiligo areas at baseline with the subject's treated areas of vitiligo at the study visit. The subject will answer the following:

> Since the start of the treatment you've received in this study, your vitiligo in areas treated with the study drug is: (1) very much improved, (2) much improved, (3) minimally improved, (4) no change, (5) minimally worse, (6) much worse, and (7) very much worse.

[redacted]

[redacted]

7.10. Other Study Procedures

7.10.1. Distribution of Subject Diaries

Starting at the Day 1 visit and each visit thereafter, a diary will be given to each subject in order to record use of the study drug. The completed diary will be collected during the subject's visit. Qualified clinical staff will review the subjects' entries for compliance. Subjects who are noncompliant with study drug (defined as not documenting diary BID use and < 70% or > 130% compliant based on prescribed application regimen and weight of study drug tubes) will have the administration instructions reinforced by the investigator or a qualified designee. Subjects will be considered compliant with the treatment regimen if they apply at least 70% but no more than 130% of the expected applications.

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definitions

For the purposes of this Protocol, an AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related, that occurs after a subject provides informed consent. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically meaningful, require therapy (eg, hematologic abnormality that requires transfusion), or require changes in the study drug(s).

8.1.2. Reporting

Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events form of the eCRF. Conditions that were already present at the time of informed consent should be recorded on the Medical History form in the eCRF. Monitoring for the occurrence of new AEs should be continued for at least 30 days after the last dose of study drug. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

The severity of AEs will be assessed using CTCAE v4.03 Grades 1 through 4. The CTCAE v4.03 severity of Grade 5 will not be used; AEs resulting in death will be graded accordingly using Grades 1 through 4 and have the outcome noted as fatal. 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:

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

The occurrence of AEs should be sought by nondirective questioning of the subject during the screening process after signing the ICF and at each visit during the study. Adverse events may also be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. To the extent possible, each AE should be evaluated to determine:

- The severity grade (CTCAE Grade 1 to 4).
- Whether there is at least a reasonable possibility that the AE is related to the study treatment: suspected (yes) or not suspected (no).

- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study drug.
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per SAE definition provided in Section 8.3.1.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements (see Section 8.3.2).

All AEs should be treated appropriately. If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on Adverse Event form and the treatment should be specified on the Prior/Concomitant Medications or Procedures and Non-Drug Therapy form in the eCRF.

Once an AE is detected, it should be followed until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat the event, and the outcome.

When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE until the event resolves. For example, 2 separate AEs will be reported if a subject has Grade 1 diarrhea, meeting the definition of an AE that lasts for 3 days before worsening to a Grade 3 severity. The Grade 1 event will be reported as an AE with a start date equal to the day the event met the Grade 1 AE definition and a stop date equal to the day that the event increased in severity from Grade 1 to Grade 3. The Grade 3 event will also be reported as an AE, with the start date equal to the day the event changed in intensity from Grade 1 to Grade 3 and a stop date equal to the day that the event either changed severity again or resolved.

8.2. Laboratory Test Abnormalities

Laboratory abnormalities that constitute an AE in their own right (considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug) should be recorded on the Adverse Event form in the eCRF. Whenever possible, a diagnosis rather than a symptom should be provided (eg, "anemia" instead of "low hemoglobin"). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory test result corresponds to a sign or symptom of a previously reported AE, it is not necessary to separately record the laboratory test result as an additional event.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A Grade 3 or 4 (severe) AE does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 8.3.1. A dose modification for the laboratory abnormality may be required (see Section 5.4) and should not contribute to the designation of a laboratory test abnormality as an SAE.

8.3. Serious Adverse Events

8.3.1. Definitions

An SAE is defined as an event that meets at least 1 of the following criteria:

- Is fatal or life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is a result of:
  - A routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
  - An elective surgery or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF.
  - A treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE and not resulting in hospital admission.
  - Any social reasons and respite care, in the absence of any deterioration in the subject's general condition.
- Results in persistent or significant disability, incapacity, or a substantial disruption of a person's ability to conduct normal life functions.
- Constitutes a congenital anomaly or birth defect.
- Is considered to be an important medical event or a medically significant 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 subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above.

8.3.2. Reporting

Every SAE, regardless of suspected causality (eg, relationship to study drug(s) or study procedure or disease progression), occurring after the subject has signed the ICF through the last study visit (or 30 days after the last dose of study drug, whichever is later) must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence, unless otherwise specified by the Protocol. Any SAEs occurring more than 30 days after the last dose of study drug should be reported to the sponsor or its designee only if the investigator suspects a causal relationship to the study drug. Information about all SAEs is collected and recorded on the Adverse Event form of the eCRF. The investigator must assess and record the causal relationship of each SAE to the study treatment. The investigator must also complete the Incyte Serious Adverse Event Report Form, in English, and send the completed and signed form to the sponsor or designee within 24 hours of becoming aware of the SAE. The investigator must provide a causality assessment, that is, assess whether there is at least a reasonable possibility that the SAE is related to the study treatment: suspected (yes) or not suspected (no). Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.

The contact information of the sponsor's study-specific representatives is listed in the investigator manual provided to each site. The original copy of the SAE Report Form and the confirmation sheet must be kept at the study site.

Investigational site personnel must report any new information regarding the SAE within 24 hours of becoming aware of the information in the same manner that the initial SAE Report Form was sent. Follow-up information is recorded on an amended or new SAE Report Form, with an indication that it is follow-up to the previously reported SAE and the date of the original report. The follow-up report should include information that was not provided on the previous SAE Report Form, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or subject 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.

If the SAE is not documented in the IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, the sponsor or its designee may urgently require further information from the investigator for reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) 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.

8.4. Emergency Unblinding of Treatment Assignment

The procedure for emergency unblinding is provided in the Study Reference Manual. This option may be used ONLY if the subject's well-being requires the investigator to be aware of the subject's treatment assignment.

The investigator has the primary right to break the blind of a subject and should try to contact the sponsor's (or its designee's) clinical research physician or medical monitor before unblinding a subject's treatment assignment; however, this is not mandatory. If a subject's treatment assignment is unblinded, then the sponsor or its designee must be notified immediately by telephone.

If an investigator, site personnel performing assessments, or subject is unblinded, then the subject must be withdrawn from the study treatment. In cases where there are ethical reasons to have the subject remain in the study, then the investigator must obtain specific approval from the sponsor's (or its designee's) clinical research physician or medical monitor for the subject to continue in the study.

8.5. Pregnancy

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

- The study drug must be discontinued immediately (female subjects only; see Section 5.4.2 for the maximum permitted duration of study drug interruption).
- 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 and breastfeeding are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form.

Any SAE occurring during pregnancy must be recorded on the SAE report form and submitted to the sponsor or designee.

8.6. Warnings and Precautions

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

8.7. Data Monitoring Committee

No external data monitoring committee will be used; however, an internal data monitoring committee will examine the interim analysis.

8.8. Product Complaints

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

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

The investigator or his/her designee is responsible for reporting a complete description of the product complaint via email or other written communication to the sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be reported as described in Section 8.1.2 of this Protocol.

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

9. STATISTICS

9.1. Study Populations

The ITT population includes all randomized subjects. Treatment groups for this population will be defined according to the treatment assignment at randomization.

The per protocol population includes randomized subjects who are considered to be sufficiently compliant with the Protocol.

The safety evaluable population includes all subjects who applied at least 1 dose of study drug. Treatment groups for this population will be determined according to the actual treatment the subject received on Day 1.

[redacted]

9.2. Selection of Sample Size

In order to provide a large safety database and to provide adequate power for efficacy variables, the total sample size for the study is 150 subjects randomized in a 1:1:1:1:1 ratio (stratified by age) to INCB018424 1.5% BID, INCB018424 1.5% QD, INCB018424 0.5% QD, INCB018424 0.15% QD, and vehicle. The sample size selection is based on the assumed response rates of 55% for the INCB018424 1.5% cream BID group, 50% for the INCB018424 1.5% cream QD group, and 5% for the vehicle group. Using a 2-sided Bonferroni corrected alpha of 0.025, 25 subjects per group will have a > 90% power to detect such a difference between either of the active treatment group and the vehicle group based on Fisher's exact test due to small expected frequency of responders in the vehicle group. Assuming a 20% dropout rate during the first 24 weeks, approximately 150 subjects will need to be randomized.

9.3. Level of Significance

A graphical procedure with gatekeeping testing strategy for the primary and key secondary analyses will be implemented. A family of 5 elementary hypotheses, corresponding to treatment comparison between each active dose group to vehicle, is evaluated in Figure 2.

9.3.1. Primary Analysis

The primary endpoint is proportion of subjects treated with INCB018424 cream who achieve a ≥ 50% improvement from baseline in F-VASI score (F-VASI50) at Week 24 compared with subjects treated with vehicle. The comparison of the primary endpoint will be performed for the superiority of either INCB018424 1.5% BID or INCB018424 1.5% QD versus vehicle (T11 and T21 in Figure 2) using the Bonferroni-Holm procedure at an overall 2-sided $\alpha = 0.05$ level. The tests on the primary endpoint will be used as a gatekeeper for 6 statistical tests on key secondary endpoints (see Figure 2).

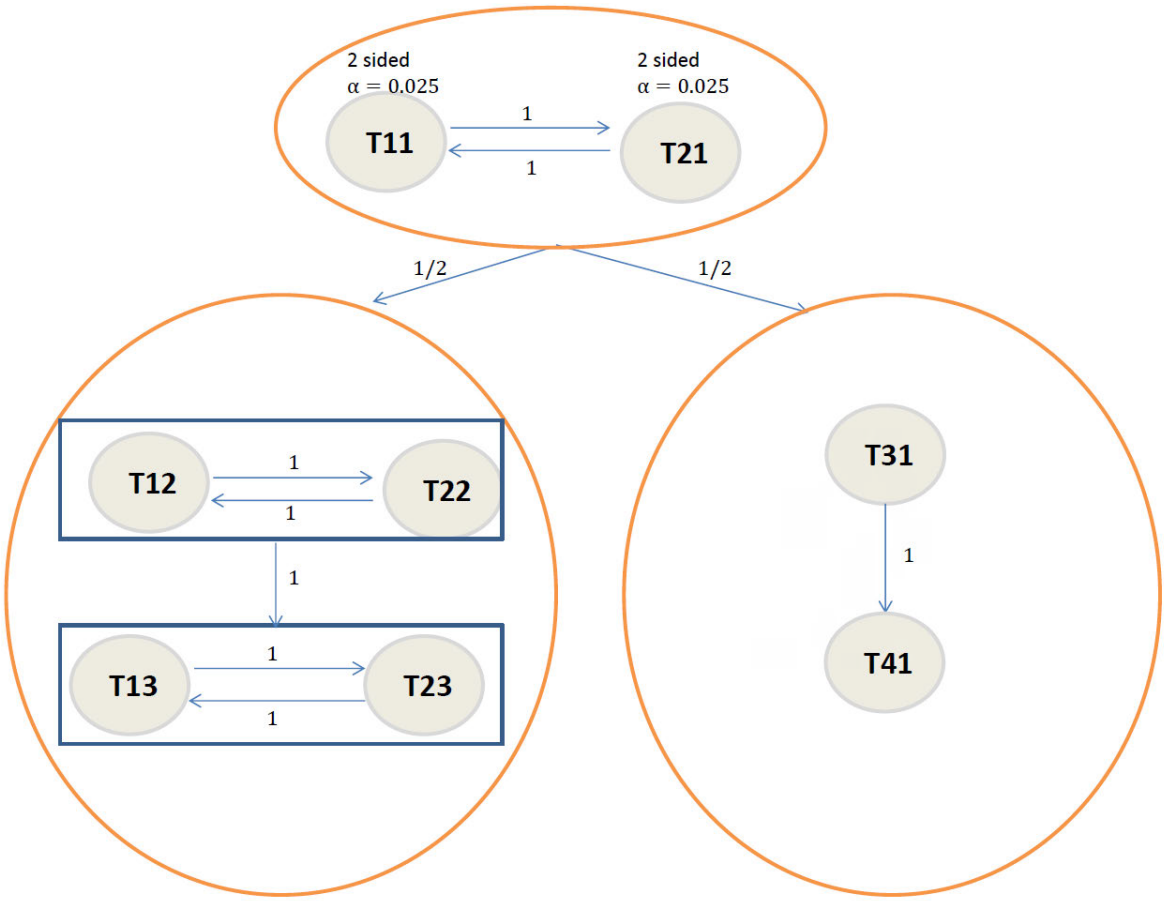
9.3.2. Secondary Analysis

The key secondary endpoint includes 6 comparisons as visualized in Figure 2.

- T31: INCB018424 0.5% QD is superior to vehicle at Week 24 on F-VASI50.
- T41: INCB018424 0.15% QD is superior to vehicle at Week 24 on F-VASI50.
- T12: INCB018424 1.5% BID is superior to vehicle at Week 24 on F-PhGVA response.
- T22: INCB018424 1.5% QD is superior to vehicle at Week 24 on F-PhGVA response.
- T13: INCB018424 1.5% BID is superior to 0.5% QD at Week 52 on VASI-50.
- T23: INCB018424 1.5% QD is superior to 0.5% QD at Week 52 on VASI-50.

The initial allocation of the overall significance level to Branch 1 (T12 and T22) and Branch 2 (T31 and T41) is 0.025, respectively. The weights of the level to be passed on if 1 hypothesis is rejected are specified in Figure 2.

Figure 2: Illustration of the Statistical Treatment Comparisons



9.3.2.1. Tests in Branch 1

The alternative hypotheses for T12 and T22 will be tested using the Bonferroni-Holm procedure at an overall 2-sided $\alpha = 0.025$ level if the null hypotheses on primary endpoints are rejected.

If both T12 and T22 are rejected, T13 and T23 will be tested using Bonferroni-Holm procedure with overall 2-sided $\alpha = 0.025$ level.

9.3.2.2. Tests in Branch 2

T31 (superiority of INCB018424 0.5% QD compared with vehicle) and T41 (superiority of INCB018424 0.15% QD compared with vehicle), will be tested sequentially at a 2-sided $\alpha = 0.025$ level if the null hypotheses on the primary endpoints are rejected.

9.4. Statistical Analyses

9.4.1. Efficacy Analyses

9.4.1.1. Efficacy Measures for Primary and Secondary Endpoints

9.4.1.1.1. VASI50 and F-VASI50

The VASI/F-VASI score is specified in Section 7.6. The categorical variable VASI50 is defined to be equal to 1 for percentage improvement from baseline in VASI/F-VASI scores of 50 or greater and 0 for less than 50. This definition is introduced for the purpose of identifying subjects who respond to the treatment (1 – responder, 0 – nonresponder).

9.4.1.1.2. Physician's Global Vitiligo Assessment

Vitiligo status will be assessed using a PGVA 5-point scale with (clear, almost clear, mild disease, moderate disease, and severe disease). A PGVA response is defined as the subjects with clear or almost clear during the treatment periods. This value will be reported for face and for overall (F-PhGVA and T-PhGVA, respectively).

9.4.1.2. Primary Efficacy Analyses

For the primary analysis, comparisons between each active group and vehicle based on F-VASI50 at Week 24 will be performed in the ITT population, with a logistic regression with treatment groups and stratification factor of baseline age. Exact logistic regression (Mehta and Patel 1995) will be used for all of the comparisons if any of the dose levels has an expected cell count less than 5. The proportions, along with unadjusted p-values and 95% confidence intervals, will be reported. All nonresponders, as well as all subjects who discontinue study treatment at any time before the timepoint of interest or discontinue from the study for any reason, will be defined as nonresponders for the nonresponder imputation analysis.

9.4.1.3. Secondary Efficacy Analyses

Secondary efficacy analyses will be conducted in the ITT population. The key secondary endpoints, including F-PhGVA response at Week 24 and T-VASI50 at Week 52, will be analyzed using the similar logistic regression as specified in the primary analysis. Unadjusted p-value will be reported, and the graphic approach will be used to control FWER. There will be no adjustment for multiple comparisons for secondary endpoints besides key secondary endpoints.

The secondary endpoints on F-PhGVA/T-PhGVA, PhGVA response, F-PaGVA/T-PaGVA, and F-VASI50/T-VASI50 at other postbaseline visits besides primary and key secondary endpoints will be summarized as categorical variables using descriptive statistics. Mean, change from baseline, and percentage change from baseline in F-VASI/T-VASI scores will be summarized using descriptive statistics. An Emax model will be fit for assessment of the dose response relationship on percentage change from baseline of F-VASI scores at Week 24, which will provide estimates of the maximum and minimum response levels, ED50 (the concentration where the response is the midpoint between the maximum and minimum), and the slope parameter. The 5 dose levels of INCB018424 cream in the model fitting will be vehicle,

0.15% QD, 0.5% QD, 1.5% QD, and 1.5% BID (equivalent to 3% QD). Mean, change from baseline, and percentage change from baseline will be summarized using descriptive statistics, including BSA (each regions and total), VETF, and target lesion size (area). The PaGIC-V response will be summarized as a categorical variable.

The Kaplan-Meier product limit method will be used to estimate time to event curves for time to response endpoints. Treatment comparisons may be performed using the log-rank test stratified by randomization stratification factor if applicable.

9.4.1.4. Other Efficacy Analyses

The other efficacy endpoints will be summarized using descriptive statistics.

9.4.2. Safety Analyses

9.4.2.1. Adverse Events

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study drug administration. Adverse events will be tabulated by the MedDRA preferred term and system organ class. Severity of AEs will be based on the National Cancer Institute CTCAE v4.03 using Grades 1 through 4.

The subset of AEs considered by the investigator to have a relationship to study drug will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study drug, then the AE will be considered treatment-related. The incidence of AEs and treatment-related AEs will be tabulated.

9.4.2.2. Clinical Laboratory Tests

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.

9.4.2.3. Vital Signs

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

[redacted]

9.5. Interim Analysis

An interim analysis will be conducted when at least half of the randomized subjects reach Week 12 and again at Week 24. The interim analyses will not include any stopping rules for futility or efficacy. There will be no external Data Monitoring Committee. Sites will remain blinded to study drug, but some personnel at Incyte without direct contact with sites will be unblinded. An internal committee will be charged with evaluating the unblinded efficacy and safety results in the interim analysis. Details will be specified in the Statistical Analysis Plan.

10. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

10.1. Investigator Responsibilities

This study will be performed in accordance with ethical principles that originate in the Declaration of Helsinki and conducted in adherence to the study Protocol; GCPs as defined in Title 21 of the US CFR Parts 11, 50, 54, 56, and 312; ICH E6 GCP consolidated guidelines; and local regulatory requirements as applicable to the study locations.

The investigator will be responsible for:

- 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 subject 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 subjects.

- 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.

- Obtaining informed consent and ensuring that the study subjects' questions have been answered and the subjects fully understand study procedures:
  - 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 subject. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to subject records.
- Obtaining approval from the IRB/IEC before the start of the study and for any changes to the clinical study Protocol, important Protocol deviations, routine updates, and safety information in accordance with institutional requirements and local law.
  - The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by the IRB/IEC.
- 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 subjects who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws, but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.

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

10.2. Accountability, Handling, and Disposal of Study Drug

The investigator is responsible for drug accountability at the study site; however, some of the drug accountability duties may be assigned to an appropriate pharmacist or other designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities. The investigator or designee must maintain records that document:

- Delivery of study drug to the study site.
- Inventory of study drug at the site.
- Subject use of the study drug including unit counts from each supply dispensed.
- Return of study drug to the investigator or designee by subjects.

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

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

10.3. Data Management

Data management will be performed in a validated database via an Electronic Data Capture (EDC) system. All data entry, verification, and validation will be performed in accordance with the current standard operating procedures of the Data Management Department at the sponsor or its designee. The database will be authorized for lock once all defined procedures are completed.

The investigator will be provided with access to an EDC system so that an eCRF can be completed for each subject. Entries made in the eCRF must be verifiable against source documents; if updates to the database are not possible, any discrepancies should be explained and documented. The investigator will be responsible for reviewing all data and eCRF entries, and will sign and date the designated forms in each subject's eCRF, verifying that the information is true and correct. The investigator is responsible for the review and approval of all query responses.

Protocol deviations will be identified and recorded in the Protocol Deviation form of 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.

10.4. Data Privacy and Confidentiality of Study Records

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

Subject names will not be supplied to the sponsor or its designee, if applicable. Only the subject number and subject's initials (subject's initials will only be recorded if allowable by local regulations) will be recorded in the eCRF, where permitted; if the subject's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that representatives of the sponsor or its designee, IRB or IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

10.5. 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 sub investigator who is directly involved in the treatment or evaluation of research subjects, including the spouse and each dependent child of the clinical investigator or sub investigator. These requirements apply to both US and foreign clinical investigators conducting covered clinical studies.

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

10.6. Publication Policy

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

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For Subjects Participating in the Study:

The following methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - injectable
  - implantable[2]
- Intrauterine device (IUD)[2]
- Intrauterine hormone-releasing system (IUS)[2]
- Bilateral tubal occlusion[2]
- Vasectomised partner[2,3]
- Sexual abstinence[4]

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

- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide[5]
- cap, diaphragm or sponge with spermicide[5]

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.
[2] Contraception methods that in the context of this guidance are considered to have low user dependency.
[3] Vasectomised partner is a highly effective method provided of avoiding pregnancy that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
[4] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
[5] A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

Source: CTFG 2014.

APPENDIX B. POTENT CYP3A4 INHIBITORS AND FLUCONAZOLE

In clinical studies with CYP3A4 inhibitors, elevated levels of INCB018424 of approximately 2-fold have been observed after oral administration. Additionally, simulations using physiologically based PK models suggested that fluconazole (a dual CYP3A4 and CYP2C9 inhibitor) increases steady-state ruxolitinib AUC by approximately 1- to 3-fold after oral administration. Thus, these concomitant medications should not be taken by subjects beginning 2 weeks or 5 half-lives (whichever is longer) before the first application of study drug until the last administration (either Week 24 or Week 52; however, topical use of these agents if the systemic bioavailability is low may be permitted on a case-by-case basis. The following is a list of potent CYP3A4 inhibitors and fluconazole. The sponsor should be contacted with any questions regarding concomitant medications that might be considered potent CYP3A4 inhibitors but are not on this list.

- boceprevir
- clarithromycin
- cobicistat
- conivaptan
- danoprevir
- elvitegravir
- fluconazole
- grapefruit juice
- idelalisib
- indinavir
- itraconazole
- ketoconazole
- LCL161
- lopinavir
- mibefradil
- nefazodone
- nelfinavir
- posaconazole
- ritonavir
- saquinavir
- telaprevir
- telithromycin
- tipranavir
- troleandomycin
- voriconazole

APPENDIX C. VITILIGO AREA SEVERITY INDEX

VASI Score range (0 - 100). Degree of depigmentation scale:

1.00 (100%) - Complete depigmentation, no pigment is present.

0.90 (90%) - Specks of pigment present.
0.75 (75%) - Depigmented area exceeds the pigmented area.
0.50 (50%) - Pigmented and depigmented areas are equal.
0.25 (25%) - Pigmented area exceeds depigmented area.
0.10 (10%) - Only specks of depigmentation present.

0.0 (0%) - No depigmentation present.

	A	**B**	**A*B**
Location	**Area involved (in hand prints)**	**Degree of depigmentation**	**Total Handprint Units**
Hands			
Upper extremities			
Trunk			
Lower extremities			
Feet			
Head/Neck			
Body Total VASI			0-100

A handprint unit (palm + 5 digits) is equal to 1% of the BSA.

APPENDIX D. VITILIGO EUROPEAN TASK FORCE SCALE

General Recommendations:

Hands and feet are included in evaluation of extent in arms and legs, but evaluated separately and globally for staging and spreading (ie, hands and feet must be staged separately/globally as one area). Staging and Spreading can be assessed simultaneously using a Wood's lamp. Use largest patch in each territory.

Recommendation to assess extent: The subject's palm including digits averages 1% BSA. Please draw the patches and mark the evaluated patches on figure below.

Recommendation to assess stage using Wood's lamp (with magnifying lens):

- Stage 0: normal pigmentation (no depigmentation in area graded)
- Stage 1: incomplete pigmentation (including spotty depigmentation, trichrome, and homogeneous lighter pigmentation)
- Stage 2: complete depigmentation, a few white hairs do not change stage
- Stage 3: partial hair whitening < 30%
- Stage 4: complete hair whitening

Recommendation to assess spreading:

- First look at patch limits using natural light.
- Second compare with Wood's lamp limits.

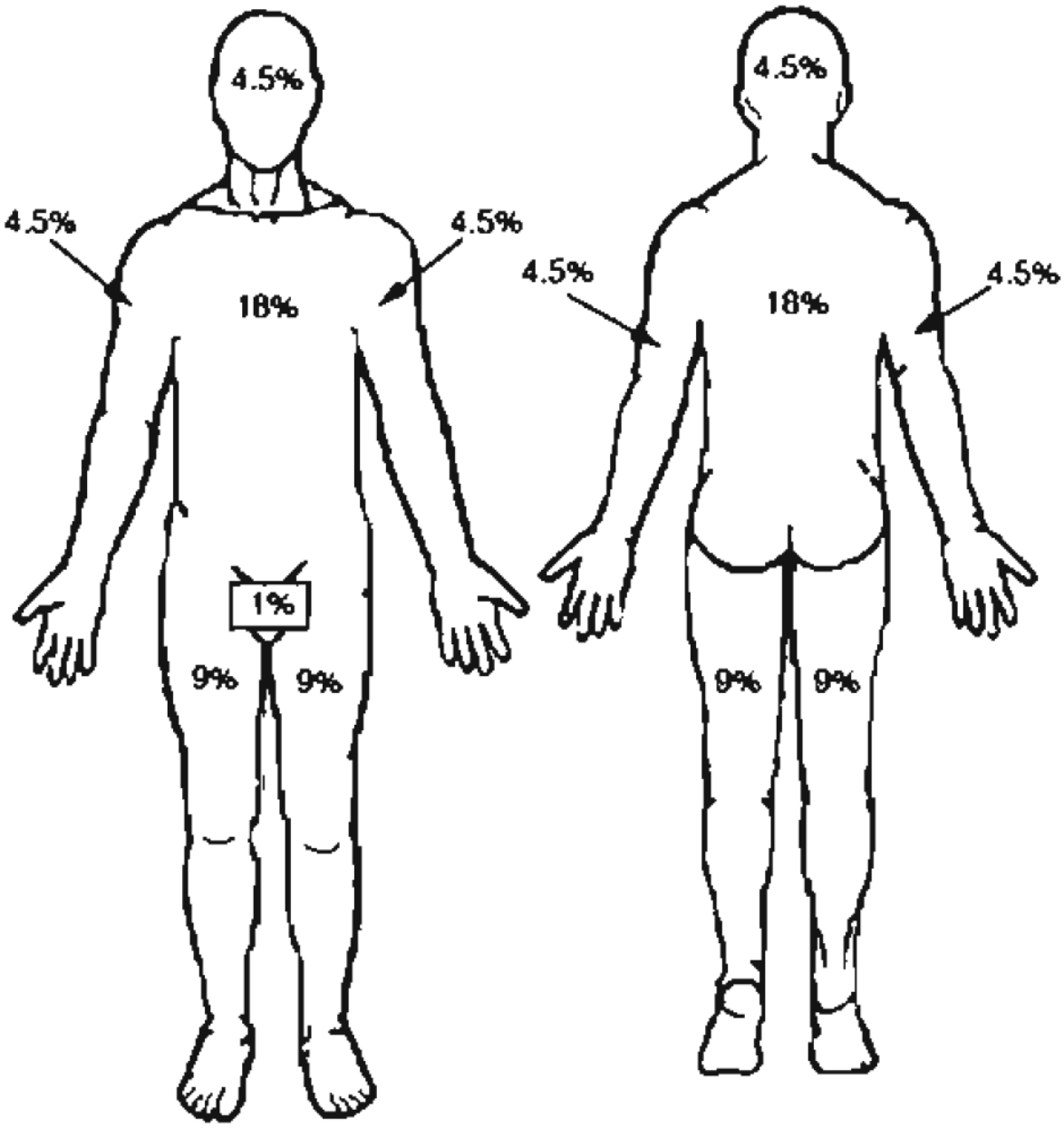
Score 0 means similar limits.

Score 1 means progressive vitiligo (ongoing subclinical depigmentation)

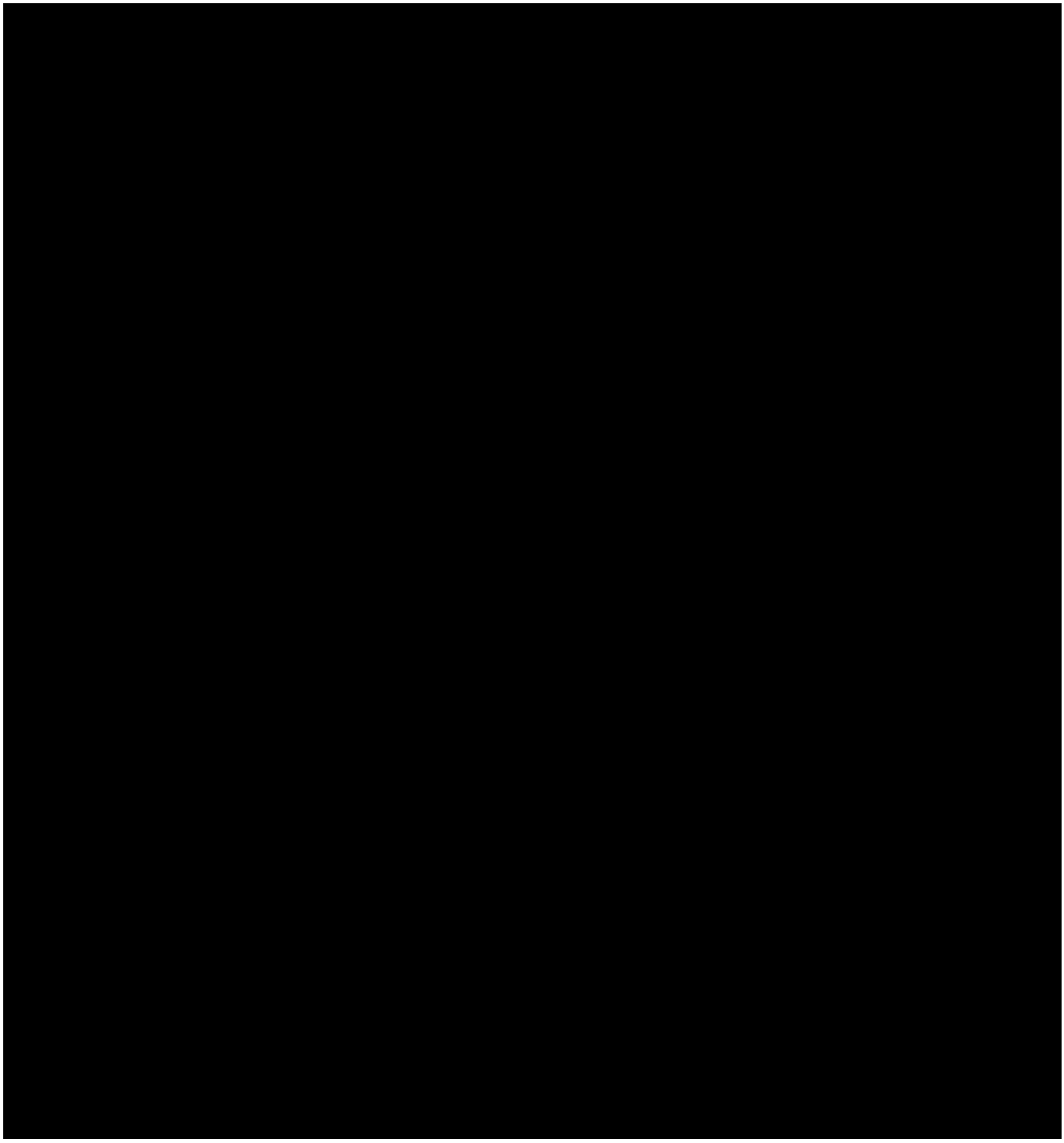
Score -1 means regressive vitiligo (ongoing subclinical repigmentation)

Area	% Area	Staging* (0–4)	Spreading* (–1 +1)
Head and neck (0–9%)			
Trunk (0–36%)			
Arms (0–18%)			
Legs (0–36%)			
Hands and feet			
Totals (0–100%)		0–20	(–5 +5)

*largest patch in each area



Source: Taïeb and Picardo 2007.



APPENDIX F. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment (Version) 1:	17 MAY 2017
Amendment (Version) 2:	08 JAN 2018
Amendment (Version) 3:	01 AUG 2019

Amendment 3 (01 AUG 2019)

Overall Rationale for the Amendment: The primary purpose of this amendment is to increase the length of the open-label extension period from 52 weeks to 104 weeks and the follow-up period from 3 months to 6 months.

1. **Synopsis; Section 1.7, Study Rationale and Justification of Dose; Section 4.1, Overall Study Design (including Figure 1: Study Design Schema); Section 4.4, Duration of Treatment and Subject Participation; Section 6, Study Assessments; Section 6.3, Treatment; Section 6.4, Follow-Up; Section 7.5.4, Electrocardiograms; Section 7.5.5.3, Urinalysis**

   Description of changes: The length of the open-label extension period was changed from 52 weeks to 104 weeks, with visits added approximately every 12 weeks during the extension period. The length of the follow-up period was changed from 3 months to 6 months. Assessments and the description of the duration of the study were updated accordingly as appropriate.

   Rationale for change: The durations of the open-label extension and follow-up periods were increased to gather information [redacted] and maintenance of response data as well as longer-term safety information.

2. **Synopsis; Section 4.1, Overall Study Design; Section 5.4.1, Dose Modifications; Section 5.4.4, Criteria and Procedures for Dose Increases of Study Drug; Section 7.6.4, Physician's Global Vitiligo Assessment**

   Description of changes: Language was updated to permit dose modifications after Week 80 for subjects who have complete facial repigmentation that is first observed after Week 80.

   Rationale for change: Since the study treatment duration has increased by an additional 52 weeks, this allows for possible modification of the dosing at additional timepoints during treatment.

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

Amendment 2 (08 JAN 2018)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to remove the enrollment cap for subjects over 30 years of age.

1. **Synopsis, Overall Study Design; Section 4.1, Overall Study Design; Section 5.1.2, Randomization and Blinding**

   Description of changes: Removed the enrollment cap for subjects over 30 years of age.

   Rationale for change: Original enrollment cap (no more than 50% of subjects) for subjects over 30 years of age is not operationally feasible and would limit the ability to deliver study results within a reasonable timeframe.

2. **Section 7.6.1, Vitiligo Area and Severity Index**

   Description of changes: Updated F-VASI and hand unit definition.

   Rationale for change: To further clarify the definition of face area and VASI measurement.

3. **Section 4.1, Overall Study Design; Section 5.1.2, Randomization and Blinding; Section 6.3, Treatment**

   Description of changes: Revised text so that the members of the primary endpoint assessment team from Incyte will be unblinded at Week 24.

   Rationale for change: To facilitate future clinical study planning.

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

Amendment 1 (17 MAY 2017)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to remove enrollment of subjects aged 12 to 17 years, and update the enrollment cap for subjects over 30 years of age to no more than 50% of subjects.

This amendment includes the changes to the Protocol INCB 18424-211 (20 JAN 2017) summarized below. A redline version of the amendment depicting the updated and previous text is also provided.

1. **Synopsis, Overall Study Design, Study Population, Key Inclusion Criteria; Section 1.7, Study Rationale and Justification of Dose; Section 3.1, Subject Inclusion Criteria; Section 4.1, Overall Study Design (Figure 1); Section 5.1.2, Randomization and Blinding**

   Description of changes: Removed subjects aged 12 to 17 years.

   Rationale for change: Study population was changed in consideration of FDA concerns that there is insufficient information from nonclinical juvenile toxicity studies at this time to assess risks in pediatric subjects.

2. **Synopsis, Overall Study Design; Section 4.1, Overall Study Design; Section 5.1.2, Randomization and Blinding**

   Description of changes: Updated enrollment cap for subjects over 30 years of age to no more than 50% of subjects.

   Rationale for change: To ensure a disease-appropriate age distribution for enrolled subjects.

3. **Section 7.6.3, Vitiligo European Task Force Scale; Appendix D, Vitiligo European Task Force Scale**

   Description of changes: Updated stage of disease (staging) in the Vitiligo European Task Force (VETF) Scale.

   Rationale for change: To make Section 7.6.3 and Appendix D consistent.

4. **Section 2.2.2, Other Secondary Endpoints; Section 9.3.2 Secondary Analysis; Section 9.4.1.3 Secondary Efficacy Analyses; Section 9.4.2.2 Clinical Laboratory Tests; 9.4.2.4 Electrocardiograms.**

   Description of changes: Corrected and updated analysis language. Shortened the Clinical Laboratory Tests section and removed the Electrocardiograms section.

   Rationale for change: To update statistical analysis language as some sections (eg, Clinical Laboratory Tests) are not applicable for a topical INCB018424 study.

[redacted]

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