Clinical Study Protocol

INCB 18424-204

An Open-Label (Part A) and a Double-Blind, Randomized, Placebo-Controlled (Part B) Study, With an Open-Label Extension, of INCB018424 Phosphate Cream Applied Topically to Subjects With Alopecia Areata

Product:	**INCB018424**
IND Number:	**77101**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Date of Protocol:	**08 MAY 2015**
Date of Amendment 1:	**14 JUL 2015**
Date of Amendment 2:	**04 FEB 2016**
Date of Amendment 3:	**29 APR 2016**
Date of Amendment 4:	**12 OCT 2016**

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 50, 54 56, 312, and Part 11 as well as ICH GCP consolidated guidelines (E6) and applicable regulatory requirements.

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for INCB018424 Cream. I have read INCB 18424-204 Protocol Amendment 4 (dated 12 OCT 2016) 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 1.5% cream (INCB018424 cream)

Title of Study: An Open-Label (Part A) and a Double-Blind, Randomized, Placebo-Controlled (Part B) Study, With an Open-Label Extension, of INCB018424 Phosphate Cream Applied Topically to Subjects With Alopecia Areata

Protocol Number: INCB 18424-204	**Study Phase:** 2

Primary Objectives:

- To evaluate preliminary efficacy of INCB018424 cream when applied twice daily (BID) to subjects with alopecia areata (AA).

Secondary Objectives:

- To evaluate the safety and tolerability of INCB018424 cream when applied BID to subjects with AA.

[redacted]

Overall Study Design:

This is a 2-part study in subjects with AA, with Part A being open-label and Part B being double-blind, randomized, and placebo-controlled.

In Part A, approximately 10 subjects will be treated with open-label topical INCB018424 1.5% cream BID for 24 weeks to examine efficacy, safety, and tolerability. Subjects with alopecia totalis, which includes alopecia universalis, will not be allowed in Part A. After completion of the Week 24 efficacy assessments, eligible subjects in Part A will be offered an additional 24 weeks of open-label treatment. To be eligible for an additional 24 weeks of open-label treatment in Part A, subjects must have completed the baseline and Week 24 Severity of Alopecia Tool (SALT) scores. Also, eligible subjects must have adequate laboratory parameters (must meet entry criteria regarding cytopenias and liver assessments) and, in the opinion of the investigator, have no additional safety concerns related to an additional 24 weeks of open-label treatment.

Part B is double-blind, randomized, and placebo-controlled, with an open-label extension in up to 68 subjects. Initially, 34 subjects will be randomized to INCB018424 1.5% cream or placebo cream, stratified by baseline percentage of scalp involvement with AA (25% to < 50% or 50% to 100%) using the revised Alopecia Areata Investigational Guidelines (rAAIG). Subjects will be treated for 24 weeks to examine efficacy, safety, and tolerability. Subjects with alopecia totalis, which includes alopecia universalis, will be limited to Part B and no more than 10% of the randomized population. Subjects with 25% to < 50% scalp involvement will be limited to no more than 70% of the randomized population in Part B. Part B will complete randomization of an additional 34 subjects if sufficient evidence of terminal hair growth is demonstrated in Part A or the interim analysis of Part B.

Sites will remain blinded to study drug, but some personnel at Incyte without direct contact with sites will be unblinded. An internal committee at Incyte will be charged with evaluating the unblinded interim results based on the futility rule, as well as considering interim safety results.

After the completion of the efficacy assessments for the primary endpoint (Week 24) in the double-blind portion of the study, treatment assignment in Part B will not be unblinded; however, all eligible subjects will be dispensed INCB018424 cream for an additional 24 weeks of open-label

treatment. To be eligible for an additional 24 weeks of open-label treatment in Part B, subjects must have completed the baseline and Week 24 SALT scores. Also, eligible subjects must have, in the opinion of the investigator, no additional safety concerns related to an additional 24 weeks of open-label treatment. All areas identified at baseline should continue to be treated through the end of the open-label extension, unless the subject has a complete clinical response.

During the first 24 weeks of treatment in Part A, if new areas of AA develop or existing areas of AA expand after baseline, subjects are NOT to apply study drug to those areas.

In Part B and in the open-label extension, if new areas of AA develop or existing areas of AA expand after baseline, subjects are permitted to apply study drug BID to those areas after a visit to document the SALT score. The visit to document the new or expanded areas may be unscheduled.

After completion of the open-label extension (48 weeks of treatment), subjects who, in the opinion of the investigator, are deriving benefit (some hair regrowth) from INCB018424 will be eligible to enter the long-term extension period for an additional 48 weeks of treatment with open-label INCB018424. Also, eligible subjects must have, in the opinion of the investigator, no additional safety concerns related to an additional 48 weeks of open-label treatment. During the long-term extension period, subjects may stop treating areas that have sufficient regrowth in the opinion of the investigator. Further, after discussion with the investigator, subjects may decrease the application rate to once daily (QD) in areas with sufficient hair regrowth.

In the open-label extension of Parts A and B or in the long-term extension, subjects who have a complete clinical response (defined as 100% terminal hair regrowth and no evidence of active hair loss) at 2 consecutive visits will stop administration and continue the open-label visits as scheduled. Subjects who have a complete clinical response who subsequently have evidence of hair loss after stopping treatment may restart treatment after a visit to document the SALT score. The visit to document the SALT score may be unscheduled.

Concomitant oral vitamins, shampoos, and hair products should remain stable during the study.

Study Drug, Dosage, and Mode of Administration:

In Parts A and B, study drug will be supplied as INCB018424 1.5% cream or placebo and will be applied topically as a thin film to the affected areas and up to 1 inch (2.5 cm) into the surrounding scalp, where evidence of a decrease in hair density or active loss as evidenced by exclamation point hairs or positive hair pull is present. Study drug should be applied in the morning and in the evening at least 10 hours apart and at least 1 hour before bedtime. All areas identified at baseline should continue to be treated through the end of the open-label extension, unless the subject has a complete clinical response. If there are new areas to be treated (either in the open-label extension of Part A or in Part B), study drug should be applied to these areas in addition to the areas identified at baseline through the end of the open-label extension. During the long-term extension period, subjects may stop treating areas that have sufficient regrowth in the opinion of the investigator. Further, after discussion with the investigator, subjects may decrease the application rate to QD in areas with sufficient hair regrowth. Application instructions will be provided at study visits and via a diary card given to the subjects. When subjects wash the treatment areas, it should be with mild soap or shampoo and water and should be pat dry before application of study drug. If used, occlusive camouflage or other contact should be avoided for at least 1 hour after an application. Subjects will be instructed to thoroughly wash hands with soap and warm water immediately after application of study drug.

Duration of Participation:

In Part A, screening is up to 28 days; open-label treatment is 24 weeks, with an additional optional 24 weeks of treatment in the open-label extension and an optional 48 weeks of treatment in the long-term extension if eligible; and follow-up is 12 weeks. Total duration is up to 112 weeks.

In Part B, screening is up to 28 days, double-blind treatment is 24 weeks, an optional open-label treatment is 24 weeks in the open-label extension and an optional 48 weeks of treatment in the long-term extension if eligible, and follow-up is 12 weeks. Total duration is up to 112 weeks.

Study Population:

Men or women, aged 18 to 70 years, who have been diagnosed with AA for at least 12 months with 25% to < 50% scalp involvement or for at least 6 months with 50% to 100% scalp involvement.

Key Inclusion Criteria:

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

- Healthy adult subjects aged 18 to 70 years, inclusive.
- Subjects diagnosed with AA and, in the opinion of the investigator, reason to believe that regrowth is possible.
- Subjects with a current episode of AA for the following durations:
  - At least 12 months before screening and involving 25% to < 50% of the scalp at baseline.
  - At least 6 months before screening and involving 50% to 100% of the scalp at baseline.
- Subjects with a positive hair pull test and/or presence of exclamation point hairs, unless subject has alopecia totalis, including alopecia universalis.
- Subjects who agree to discontinue all agents used to treat AA from screening through the final follow-up visit; use of over-the-counter preparations (including vitamins, minerals, phytotherapeutic/herbal/plant-derived preparations, and other hair products) deemed acceptable by the investigator are permitted.

Key Exclusion Criteria:

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

- Part A only: Subjects with a current diagnosis of alopecia universalis, alopecia totalis, or only ophiasis type AA.
- Subjects with a current episode of alopecia universalis or alopecia totalis of more than 2 years in duration.
- Subjects with evidence of diffuse, spontaneous terminal hair regrowth at screening and/or baseline.
- Subjects with a history of complete spontaneous remission in the prior 2 years.
- Subjects who have received treatment known to potentially affect the course of AA within 1 month before the baseline visit (eg, topical and intralesional corticosteroids, oral or topical minoxidil).
- Subjects taking immunosuppressive medications (including topical agents) for any concurrent illness, except inhaled corticosteroids for asthma and allergic rhinitis, and 1% topical hydrocortisone or alternate Class 7 topical steroid for atopic dermatitis/eczema for areas outside the scalp any time after screening.
- Subjects taking systemic retinoids, etanercept, adalimumab, efalizumab, alefacept, other biological therapies, or immunosuppressives (eg, corticosteroids [oral or injectable], methotrexate, cyclosporine) within 6 weeks before the baseline visit.
- Subjects taking systemic potent CYP3A4 inhibitors or fluconazole within 2 weeks or 5 half-lives, whichever is longer, before the baseline visit.
- Subjects with a history of medical disorders (eg, autoimmune diseases) whose treatments could complicate the assessment of hair loss on the scalp, except for:
  - Thyroid disease on stable treatment for at least 6 months before screening.
  - Asthma on stable treatment for at least 3 months before screening.
- Subjects with an abnormal TSH or free T4 at screening.
- Subjects with cytopenias at screening, defined as:
  - Leukocytes < 3×10^9/L.
  - Neutrophils < lower limit of normal.

  - Lymphocytes < lower limit of normal.
  - Hemoglobin < 10 g/dL.
  - Platelets < 100×10^9/L.
- Subjects with severely impaired liver function (Child-Pugh Class C) or end-stage renal disease on dialysis or at least 1 of the following:
  - Serum creatinine > 1.5 mg/dL.
  - Alanine aminotransferase or aspartate aminotransferase ≥ 1.5 × upper limit of normal.
- Positive serology test results for hepatitis B surface antigen or core antibody, or for hepatitis C virus antibody with detectable hepatitis C RNA at screening.

Study Schedule/Procedures:

All subjects in Parts A and B will have visits at screening, baseline, and Weeks 4, 8, 12, 18, and 24. All subjects in Parts A and B will have similar assessments, except as noted below.

Adverse events (AEs), medication history, clinical assessments, physical exam, vital signs, and clinical safety laboratories (including reticulocyte count) will be performed at each visit. All laboratory assessments will be performed using a central laboratory except for urine pregnancy tests (as applicable).

Scalp photography will be performed at baseline and Weeks 12 and 24, and also at Week 4 in Part A.

[redacted]

Study drug will be applied in the clinic on the day of a study visit based on the scalp surface area involved with AA and up to 1 inch (2.5 cm) into the surrounding scalp, where evidence of a decrease in hair density or active loss as evidenced by exclamation point hairs or positive hair pull is present. Subjects will be instructed to bring all study drug tubes with them to each visit so that compliance can be assessed. At Week 24, compliant subjects with baseline and Week 24 SALT scores will be offered an optional 24 weeks of open-label treatment.

Subjects in the open-label extension period of Part A will have study visits every 6 weeks during Weeks 30 to 48. Subjects in Part B who enter the open-label extension period will have study visits at Weeks 28, 32, 36, 42, and 48. Scalp photography will be performed at Weeks 36 and 48.

During the open-label extension period, following the Week 24 visit, subjects with a complete clinical response (defined as 100% terminal hair regrowth and no evidence of active hair loss at 2 consecutive visits, which may include visits during the double-blind period) will stop applying study drug and will continue the scheduled visits in the open-label period. These subjects will then have the follow-up assessments 1 and 3 months after the Week 48 visit.

Subjects in the long-term extension period will have study visits at Weeks 60, 72, 84, and 96.

After the end-of-treatment visit, subjects will have follow-up assessments 1 and 3 months later to monitor for [redacted] AE, medication history, vital signs, and clinical assessments, and scalp photography at the 3-month follow-up visit. If other treatment for AA is started, an earlier 3-month follow-up visit will be performed as a final, and thus end of study visit. If needed, a follow-up phone call will be conducted to determine any AEs or serious adverse events during the 30 days after the last dose of study drug.

Part A:

Primary Endpoints:

- Percentage of subjects achieving a ≥ 50% improvement in Severity of Alopecia Tool (SALT50) response in terminal hair (pigmented and nonpigmented) at any visit up to Week 24 (inclusive).

Secondary Endpoints:

- Percentage of subjects with 50% to 100% scalp involvement at baseline achieving a SALT50 response in terminal hair at any visit through Week 24.
- Percentage of subjects achieving a SALT90 response in terminal hair at Weeks 4, 8, 12, 18, and 24.
- Safety and tolerability assessed by monitoring the frequency, duration, and severity of AEs; performing physical examinations; collecting vital signs; and collecting laboratory data for hematology, serum chemistry, and urinalysis.

[redacted]

Part B:

Primary Endpoint:

- Percentage of subjects achieving a SALT50 response in terminal hair (pigmented and nonpigmented) at Week 24.

Secondary Endpoints:

- Percentage of subjects whose AA lesions treated since baseline achieved a Physician's Global Assessment of Regrowth (PGARG) score of at least 3 (0, no regrowth; 1, < 25% of regrowth; 2, 25%-49% of regrowth; 3, 50%-74% of regrowth; 4, 75%-99% of regrowth; 5, 100% of regrowth) using live evaluations compared to baseline photographs at Week 24.
- Percentage of subjects with 50% to 100% scalp involvement at baseline achieving a SALT50 response in terminal hair (pigmented and nonpigmented) at Week 24.
- Percentage of subjects achieving a SALT50 in terminal hair (pigmented and nonpigmented) at Weeks 4, 8, 12, and 18.
- Percentage of subjects achieving a SALT90 in terminal hair (pigmented and nonpigmented) at Weeks 4, 8, 12, 18, and 24.
- Mean change from baseline in SALT score at Weeks 4, 8, 12, 18, and 24.
- Safety and tolerability assessed by monitoring the frequency, duration, and severity of AEs; performing physical examinations; collecting vital signs; and collecting laboratory data for hematology, serum chemistry, and urinalysis.

[redacted]

Planned Number of Subjects: Part A will enroll up to approximately 10 subjects. Part B will enroll up to approximately 68 subjects.

Planned Number of Study Sites: Part A will include 1 to 5 sites. Part B will include 10 to 20 sites.

Principal Coordinating Investigator: [redacted], MD, [redacted]

Statistical Methods:

In Part A, the sample size is based on the demonstration of preliminary findings of hair regrowth. It is anticipated that a sample of 10 subjects will permit sufficient data to decide to enroll more than 34 subjects in Part B (required for interim analysis).

In Part B, the sample size calculation is based on the Fisher exact test for the primary efficacy endpoint assuming a small expected frequency of responders in the placebo group, given the low response rate. For subjects with 25% to < 50% and 50% to 100% scalp involvement, the response rate is assumed to be 61% for active versus 25% for placebo, and 35% for active versus 5% for placebo, respectively. Using a 2-sided alpha of 0.05 with a continuity correction, 34 subjects per group will have an 80% power to detect a difference between treatment groups.

The response rate assessed based on SALT50 between active- and placebo-treated subjects will be compared using a logistic regression with covariates of baseline SALT score and stratification factor of rAAIG group. The clinical safety data (vital signs, routine laboratory tests, and AEs) will be analyzed using descriptive statistics (eg, mean, frequency).

The INCB018424 plasma concentration data collected at study visits will be analyzed using summary statistics.

All secondary [redacted] efficacy measures will be evaluated using descriptive statistics. Subjects will be stratified at randomization into 2 groups: 25% to < 50% scalp involvement (rAAIG Group S2) and 50% to 100% scalp involvement (rAAIG Groups S3, S4, and S5).

Subjects with alopecia totalis (group S5), which includes alopecia universalis, will not be allowed in Part A and will be limited to no more than 10% of the randomized population in Part B.

Subjects with 25% to < 50% scalp involvement will be limited to no more than 70% of the randomized population in Part B.

An interim analysis will be performed when 34 subjects in Part B have 12-week data available and a test for futility will be performed. Sites will remain blinded to study drug but some personnel at the sponsor (without direct contact with sites) will be unblinded. Part B will complete randomization of additional subjects if sufficient evidence of terminal hair growth is demonstrated either at the interim analysis in Part A or at one of the interim analyses of Part B, or in an additional interim analysis if 1 group of subjects is under represented in the first interim analysis of Part B. An additional interim analysis may be conducted when 24-week data are available for half of the subjects in Part B. The interim analysis will not include any testing for futility or efficacy.

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LIST OF ABBREVIATIONS

Term	Explanation
AA	alopecia areata
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BID	twice daily
BSA	body surface area
CFR	Code of Federal Regulations
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
EOT	end of treatment
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HCV-RNA	hepatitis C virus ribonucleic acid
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN-γ	interferon-γ
IL	interleukin
IN	Investigator Notification
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	intent-to-treat
JAK	Janus kinase
LC/MS/MS	liquid chromatography-tandem mass spectrometry

Term	Explanation
MedDRA	Medical Dictionary for Regulatory Activities
NK	natural killer
NOAEL	no-observed-adverse-effect level
PGARG	Physician's Global Assessment of Regrowth
PK	pharmacokinetic
PV	polycythemia vera
QD	once daily
rAAIG	revised Alopecia Areata Investigational Guidelines
SAE	serious adverse event
SALT	Severity of Alopecia Tool
SALT50	≥ 50% improvement in Severity of Alopecia Tool
SALT90	≥ 90% improvement in Severity of Alopecia Tool
STAT	signal transducers and activators of transcription
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal

1. INTRODUCTION

INCB018424 cream is a topical formulation of INCB018424 phosphate under development for the treatment of patients with psoriasis and alopecia areata (AA). INCB018424 phosphate is an inhibitor of the Janus kinase (JAK) family of protein tyrosine kinases. Isogenic and inflammatory cytokines are strongly implicated in the pathogenesis of psoriasis and AA. Because JAKs serve to translate extracellular signals from a number of relevant cytokines and growth factors upregulated in inflammatory diseases such as psoriasis and AA, JAK inhibitors represent potential therapeutic agents for these disease states.

1.1. Alopecia Areata

Alopecia areata is the most frequent cause of inflammation-induced hair loss, affecting an estimated 4.5 million people in the United States (Gilhar et al 2012). Alopecia areata was noted to have a prevalence of approximately 0.1% to 0.2%, with a lifetime risk of 1.7% (Safavi et al 1995), and the vast majority of affected individuals are 30 years old or younger at the time of disease onset. Although not life threatening, the disease is an affliction, particularly to people with extensive disease including complete hair loss of the scalp (alopecia totalis) and scalp and body (alopecia universalis). In general, hair is lost from the scalp in bald patches. In most cases, the loss of hair is in well-circumscribed patches of normal-appearing skin, most commonly on the scalp and in the region of the beard. The number of people with AA who go on to develop alopecia totalis or alopecia universalis is unknown, but estimates range from 7% to 30% (Bolduc 2014).

Individuals with AA are subject to rapid and dramatic changes in their appearance caused by the sporadic hair loss. The aesthetic repercussions can lead to profound negative changes in patient's psychological status and relationships, with a high prevalence of anxiety and depressive symptoms in AA patients (Ghanizadeh and Ayoobzadehshirazi 2014).

Curative therapy does not exist, and there is a lack of long-term, controlled studies evaluating therapy for AA and its effect on quality of life. There are 2 principal management options: use of an immunosuppressive regimen, such as intralesional injections or topical application of glucocorticoids, or an immune-deviation strategy that manipulates the intracutaneous inflammatory milieu through the induction of contact allergy. Topical glucocorticoids lead to at least 50% regrowth in 41% of those with at least 50% loss at baseline (Olsen 1997). However, treatment is associated with side effects such as glucocorticoid-induced folliculitis and localized skin atrophy. The use of systemic glucocorticoids is also limited because of the adverse event (AE) profile. All treatments for AA have the potential for further loss after discontinuation of therapy in the cases where regrowth is incomplete at the time of discontinuation of treatment. New approaches that increase regrowth in cases of AA without introducing safety issues are needed.

1.2. Autoimmunity and Alopecia Areata

In acute AA, histologic examination reveals a characteristic pattern of dense, perifollicular lymphocytic infiltrates around anagen hair follicles, suggesting an immunological basis for the hair loss. CD4+ T cells predominate in the perifollicular infiltrates, while CD8+ T cells appear

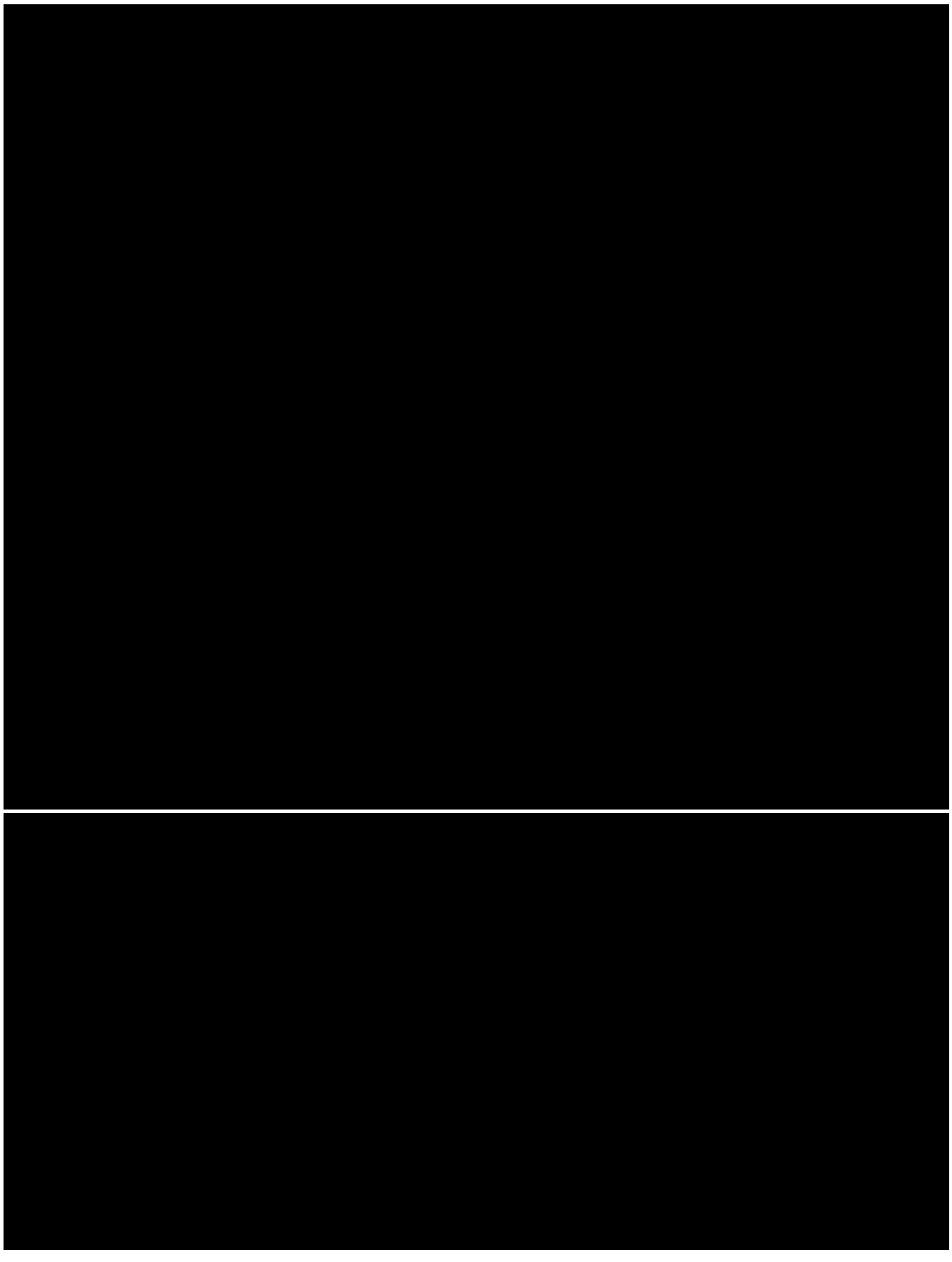
to be the first lymphocytes to enter the proximal follicular epithelium. In addition, the numbers of natural killer (NK) cells and mast cells are greatly increased in the perifollicular infiltrates. It has been found that individuals with AA have higher rates of other autoimmune diseases, supporting an underlying immune activation that leads to hair loss (Petukhova and Christiano 2013). Alopecia areata occurs more frequently in people who have affected family members, suggesting heredity may be a factor (Bolduc 2014). Alopecia areata has been linked with certain human leukocyte antigen class II alleles, as have many autoimmune diseases. A genome-wide association study (Jagielska et al 2012) showed a strong association of predisposition to AA with polymorphisms of ligands for the NK cell–activating receptor NKG2D. In this analysis, T lymphocytes, as well as members of the γc cytokine-receptor pathway and interferon-γ (IFN-γ), which signal through the JAK–signal transducers and activators of transcription (STAT) pathway, were also implicated in AA.

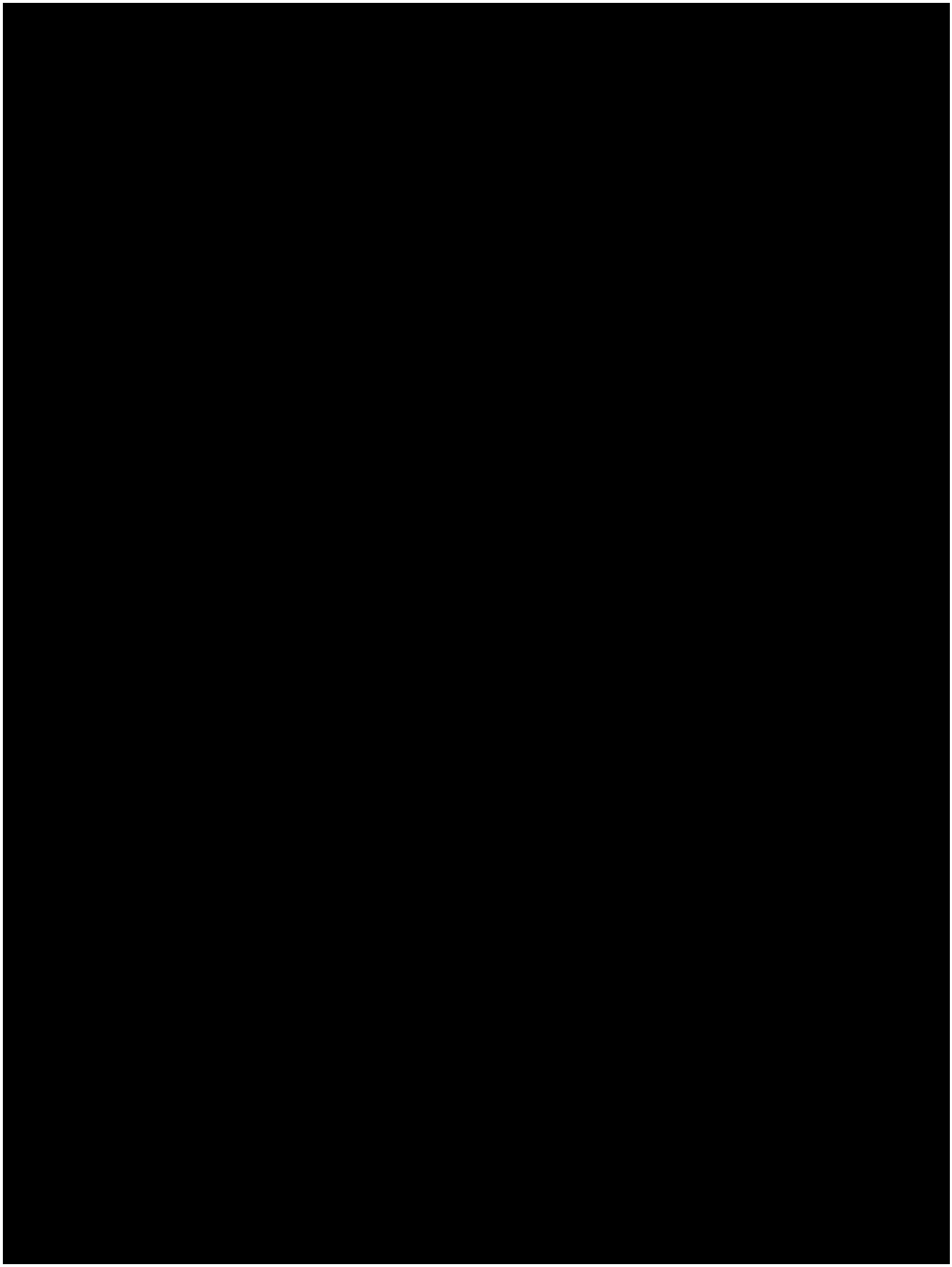
Xing et al (2014) has presented further evidence supporting autoimmunity as the underlying cause using a spontaneous mouse model of AA. Using this model, they demonstrated that AA is mediated by CD8+NKG2D+ T cells via an interleukin (IL)-15 positive feedback loop. The AA phenotype could be adoptively transferred to normal mice via transfer of lymph node preparations or positively selected CD8+NKG2D+ T cells.

1.3. Role of JAKs in Alopecia Areata

Xing et al (2014) performed comparative genomics of the transcriptional profiles of skin from both AA model mice and humans with AA. This study provided evidence for the involvement of γc cytokines, including IL-2, IL-7, IL-15, and IL-21, and IFN-γ response elements with increased JAK1 and JAK3 expression in diseased human and mouse skin. In the mouse model, they demonstrated that systemic administration of antibodies to the JAK-dependent cytokines IL-2, IL-15R, or IFN-γ blocked AA development. Notably, blocking antibodies against IL-2, IL-15R, and IFN-γ, when given individually, did not reverse established AA in mice, and therefore a broader inhibition strategy that modulates multiple cytokines may represent a viable treatment strategy. Since each of these cytokines signals through the JAK-STAT pathway, treatment of AA with JAK inhibitors may represent a preferred treatment strategy. Xing et al (2014) investigated small-molecule inhibitors of JAK both systemically and topically and showed that they could arrest and reverse AA in the mouse model. Global transcriptional analysis showed reduced inflammation in skin of mice treated with JAK inhibitors. Supporting human data for this has come from treatment of subjects with AA with oral JAK1/2 inhibitors. Treatment reversed established AA and resulted in a reduction in inflammation in the subjects' skin biopsies.

The unpredictable course of AA with localized hair loss and spontaneous remissions frequently occurring makes it challenging to design and conduct studies, particularly with systemic therapies. Because AA is a skin-associated disease and there are hematological liabilities associated with systemic JAK inhibition, topical JAK inhibitors seem to be a very promising approach, particularly for localized disease. To date, a topical JAK inhibitor with sufficient skin penetration has not yet been developed in AA. The JAK1/2 inhibitor INCB018424 has been used systemically successfully in myeloproliferative disorders, and a topical formulation of INCB018424 has been developed and demonstrated to be active in patients with psoriasis.





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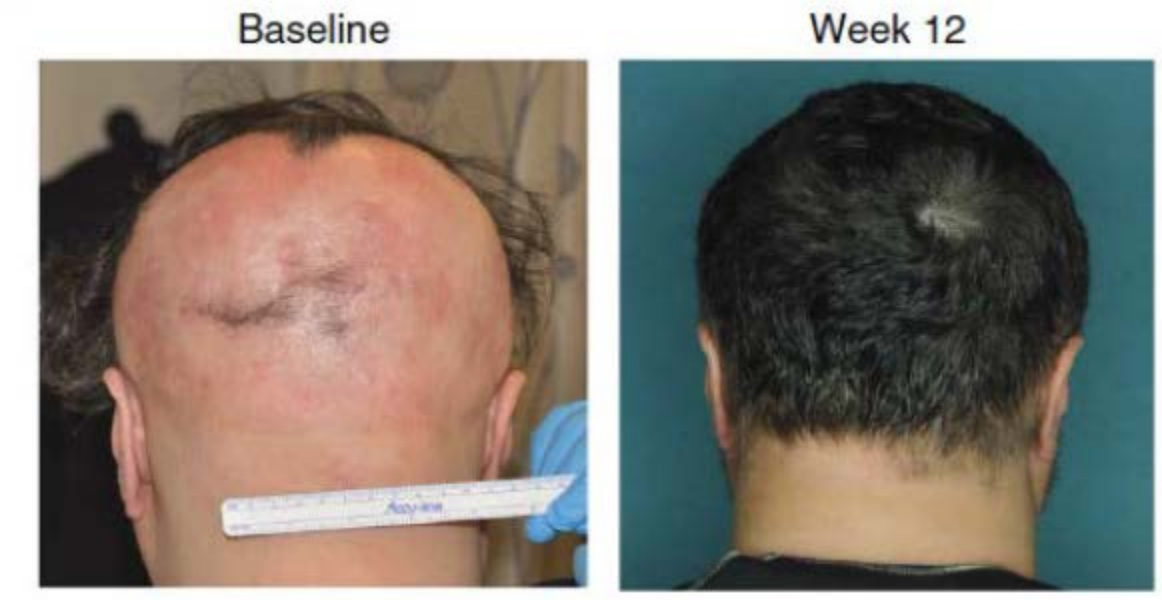
1.7. Clinical Experience

1.7.1. Clinical Efficacy With Oral INCB018424 in Alopecia Areata

Three subjects treated with oral INCB018424 (ruxolitinib) achieved near-complete hair regrowth within 5 months of treatment (Xing et al 2014). A photograph of 1 patient with > 80% AA at baseline is pictured below at baseline and after 12 weeks of treatment.



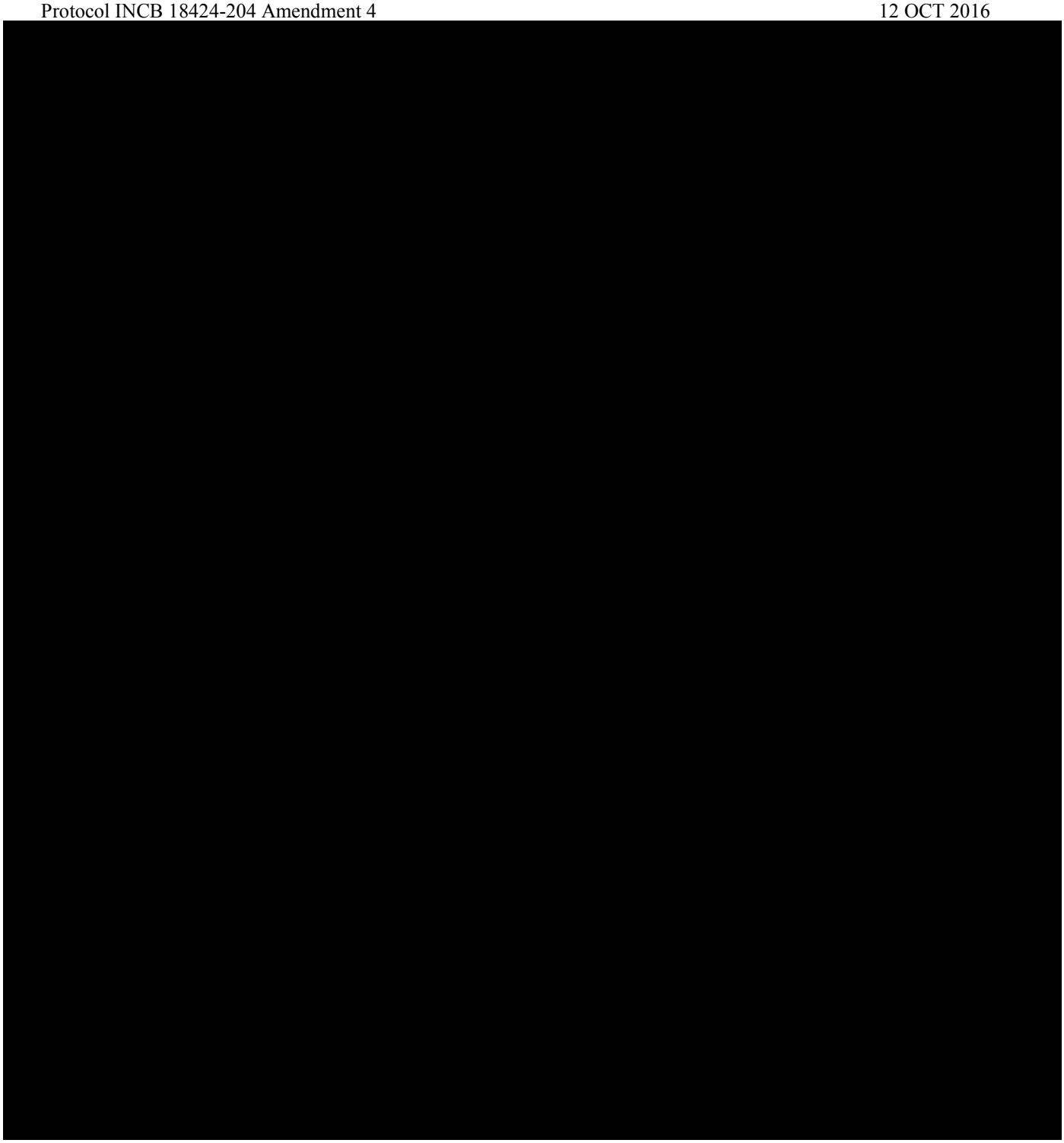
1.7.2. Clinical Efficacy With Topical INCB018424 in Psoriasis

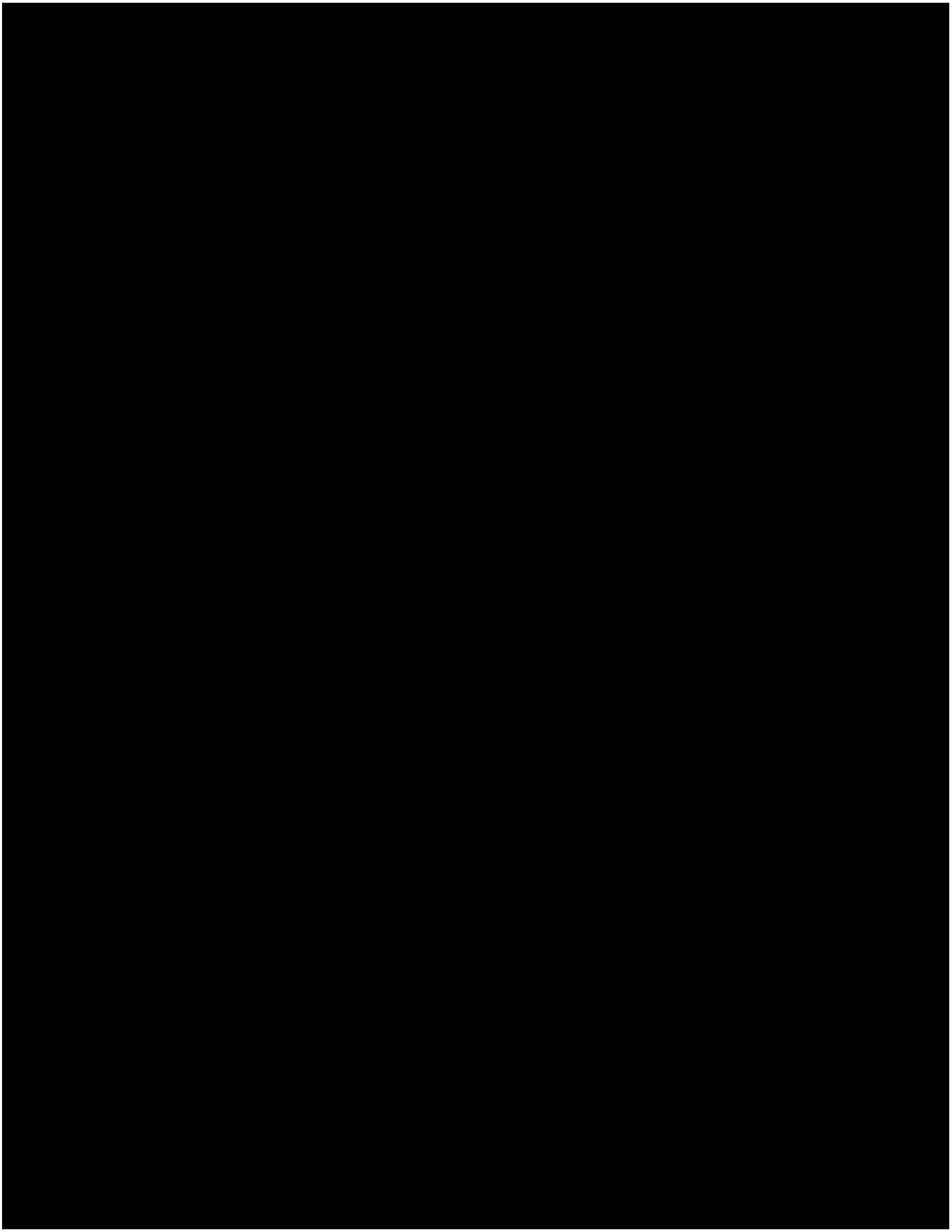
In a double-blind, vehicle- or comparator-controlled, ascending dose, safety, tolerability, PK, and preliminary efficacy study of INCB018424 cream in subjects with plaque psoriasis (Study INCB 18424-201), efficacy was demonstrated with both the 1% cream applied QD and the 1.5% cream applied BID with 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.

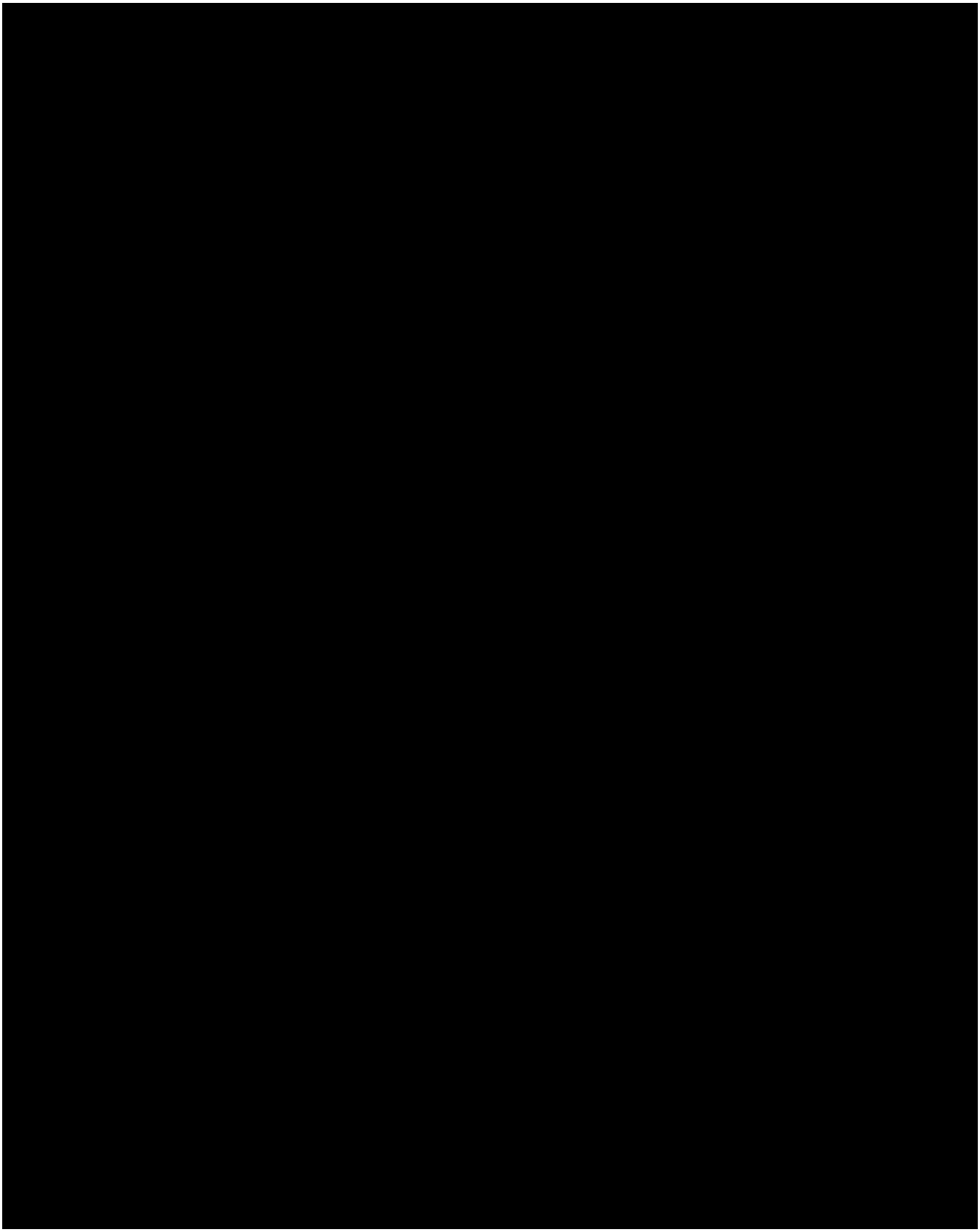
In an open-label, multicenter, sequential-cohort, dose-escalation, safety, tolerability, PK, pharmacodynamic, and preliminary efficacy study of INCB018424 1% or 1.5% cream applied to 2% to 20% BSA QD or BID for 4 weeks in subjects with active, stable plaque psoriasis (Study INCB 18424-202), the efficacy analyses collectively revealed that all 5 regimens of INCB018424 cream, when applied for 28 days, were effective in decreasing the individual signs of lesion severity, lesion area, and the overall disease severity of psoriatic plaques. Within each cohort, the mean individual and total psoriasis assessment scores for the treated lesions decreased from baseline to each subsequent assessment, indicating an overall lessening of disease severity.

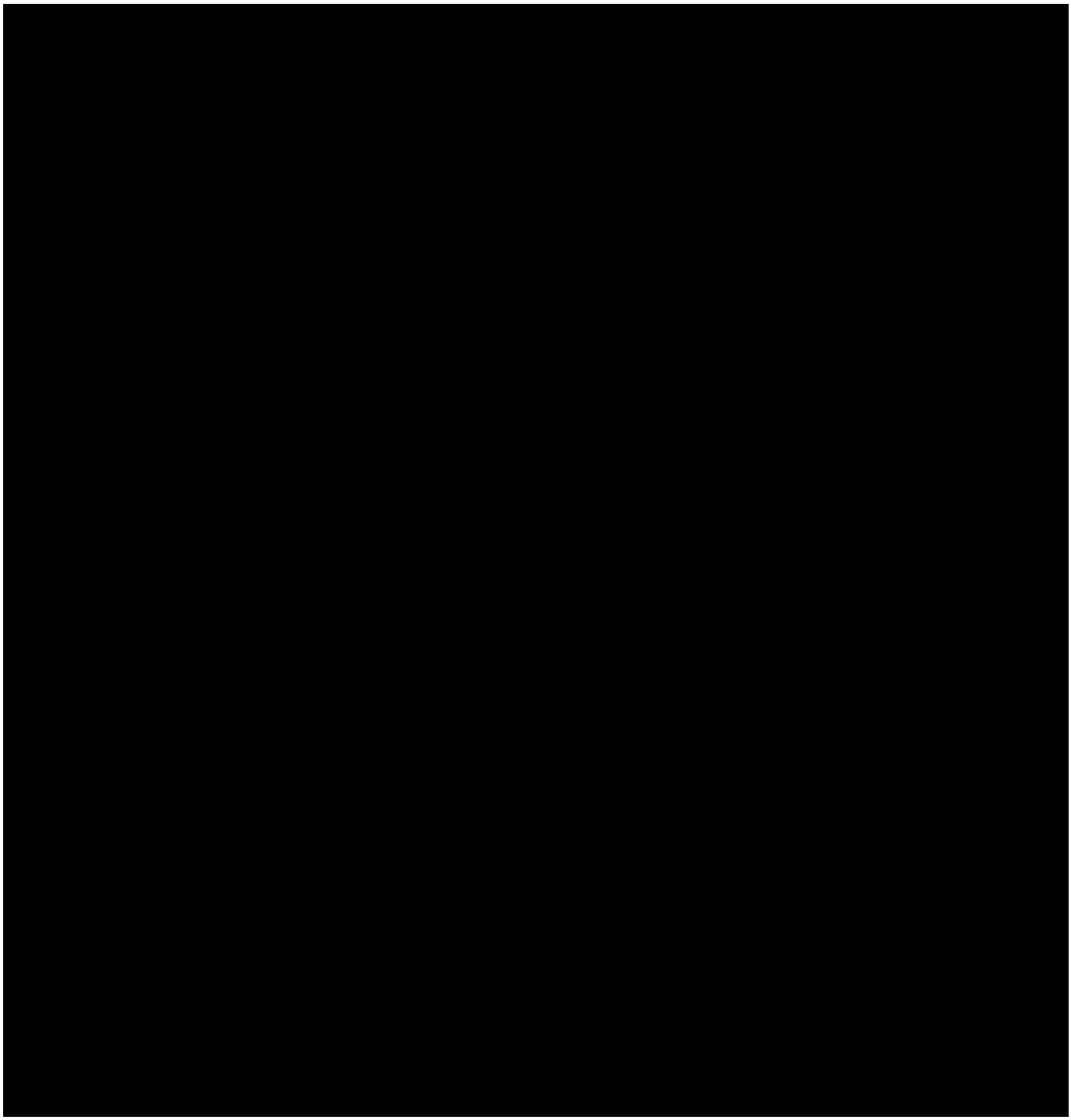
The total lesion scores for the control lesions within each cohort either increased from baseline, indicating a worsening of disease severity, or decreased marginally from baseline.

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 PGA, 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.









1.7.5. 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 aminotransferase (ALT; 27.2%), increased aspartate aminotransferase (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 cut-off 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 polycythemia vera (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.

[redacted]

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

- To evaluate preliminary efficacy of INCB018424 cream when applied BID to subjects with AA.

2.1.2. Secondary Objectives

- To evaluate the safety and tolerability of INCB018424 cream when applied BID to subjects with AA.

[redacted]

2.2. Study Endpoints

2.2.1. Primary Endpoints

2.2.1.1. Part A

- Percentage of subjects achieving a ≥ 50% improvement in Severity of Alopecia Tool (SALT50) response in terminal hair (pigmented and nonpigmented) at any visit up to Week 24 (inclusive).

2.2.1.2. Part B

- Percentage of subjects achieving a SALT50 response in terminal hair (pigmented and nonpigmented) at Week 24.

2.2.2. Secondary Endpoints

2.2.2.1. Part A

- Percentage of subjects with 50% to 100% scalp involvement at baseline achieving a SALT50 response in terminal hair at any visit through Week 24.
- Percentage of subjects achieving a SALT90 response in terminal hair at Weeks 4, 8, 12, 18, and 24.
- Safety and tolerability assessed by monitoring the frequency, duration, and severity of AEs; performing physical examinations; collecting vital signs; and collecting laboratory data for hematology, serum chemistry, and urinalysis.

2.2.2.2. Part B

- Percentage of subjects whose AA lesions treated since baseline achieved a Physician's Global Assessment of Regrowth (PGARG) score of at least 3 (0, no regrowth; 1, < 25% of regrowth; 2, 25%-49% of regrowth; 3, 50%-74% of regrowth; 4, 75%-99% of regrowth; 5, 100% of regrowth) using live evaluations compared to baseline photographs at Week 24.
- Percentage of subjects with 50% to 100% scalp involvement at baseline achieving a SALT50 response in terminal hair (pigmented and nonpigmented) at Week 24.
- Percentage of subjects achieving a SALT50 in terminal hair (pigmented and nonpigmented) at Weeks 4, 8, 12, and 18.
- Percentage of subjects achieving a SALT90 in terminal hair (pigmented and nonpigmented) at Weeks 4, 8, 12, 18, and 24.

- Mean change from baseline in SALT score at Weeks 4, 8, 12, 18, and 24.
- Safety and tolerability assessed by monitoring the frequency, duration, and severity of AEs; performing physical examinations; collecting vital signs; and collecting laboratory data for hematology, serum chemistry, and urinalysis.

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. Healthy adult subjects aged 18 to 70 years, inclusive.
2. Subjects diagnosed with AA and, in the opinion of the investigator, reason to believe that regrowth is possible.
3. Subjects with a current episode of AA for the following durations:
    a. At least 12 months before screening and involving 25% to < 50% of the scalp at baseline.
    b. At least 6 months before screening and involving 50% to 100% of the scalp at baseline.
4. Subjects with a positive hair pull test and/or presence of exclamation point hairs, unless subject has alopecia totalis, including alopecia universalis.
5. Subjects who agree to discontinue all agents used to treat AA from screening through the final follow-up visit; use of over-the-counter preparations (including vitamins, minerals, phytotherapeutic/herbal/plant-derived preparations, and other hair products) deemed acceptable by the investigator are permitted per Sections 5.8.2 and 5.8.3.
6. Willingness to avoid pregnancy or fathering children based on the criteria below:
    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).
    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 (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective 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 (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective 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 informed consent form (ICF).

3.2. Subject Exclusion Criteria

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

1. Part A only: Subjects with a diagnosis of alopecia universalis, alopecia totalis, or only ophiasis type AA.
2. Subjects with a current episode of alopecia universalis or alopecia totalis of more than 2 years in duration.
3. Subjects with evidence of diffuse, spontaneous terminal hair regrowth at screening and/or baseline.
4. Subjects with a history of complete spontaneous remission in the prior 2 years.
5. Subjects who have received treatment known to potentially affect the course of AA within 1 month before the baseline visit (eg, topical and intralesional corticosteroids, oral or topical minoxidil).
6. Subjects taking immunosuppressive medications (including topical agents) for any concurrent illness, except inhaled corticosteroids for asthma and allergic rhinitis, and 1% topical hydrocortisone or alternate Class 7 topical steroid for atopic dermatitis/eczema for areas outside the scalp any time after screening.
7. Subjects taking systemic retinoids, etanercept, adalimumab, efalizumab, alefacept, other biological therapies, or immunosuppressives (eg, corticosteroids [oral or injectable], methotrexate, cyclosporine) within 6 weeks before the baseline visit.
8. Subjects taking systemic potent CYP3A4 inhibitors or fluconazole within 2 weeks or 5 half-lives, whichever is longer, before the baseline visit (see Appendix C).
9. Subjects with a history of medical disorders (eg, autoimmune diseases) whose treatments could complicate the assessment of hair loss on the scalp, except for:
    a. Thyroid disease on stable treatment for at least 6 months before screening.
    b. Asthma on stable treatment for at least 3 months before screening.
10. Subjects with an abnormal TSH or free T4 at screening.
11. Subjects with cytopenias at screening, defined as:
    a. Leukocytes $< 3 \times 10^9$/L.
    b. Neutrophils < lower limit of normal.
    c. Lymphocytes < lower limit of normal.
    d. Hemoglobin < 10 g/dL.
    e. Platelets $< 100 \times 10^9$/L.
12. Subjects with severely impaired liver function (Child-Pugh Class C) or end-stage renal disease on dialysis or at least 1 of the following:
    a. Serum creatinine > 1.5 mg/dL.
    b. Alanine aminotransferase or AST $\geq 1.5 \times$ upper limit of normal (ULN).
13. Positive serology test results for hepatitis B surface antigen or core antibody, or for hepatitis C virus antibody with detectable hepatitis C RNA at screening.

14. Women who were pregnant or breastfeeding within 4 months before screening.
15. Current or recent history (< 30 days before screening and/or < 45 days before randomization) of a clinically meaningful bacterial, fungal, parasitic, or mycobacterial infection.
16. Current clinically meaningful viral infection, including known human immunodeficiency virus 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).
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 5.8.3) 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 who have previously received JAK inhibitors.
24. Subjects with a history of malignancy, except for the following adequately treated, nonmetastatic malignancies: basal cell skin cancer not involving the scalp, squamous cell carcinomas of the skin not involving the scalp, or *in situ* cervical cancer.
25. Subjects who have received chemotherapy.
26. Subjects who anticipate receiving a live or live-attenuated vaccination from screening through the final follow-up visit.
27. 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 2-part study in subjects with AA, with Part A being open-label and Part B being double-blind, randomized, and placebo-controlled.

In Part A, approximately 10 subjects will be treated with open-label topical INCB018424 1.5% cream BID for 24 weeks to examine efficacy, safety, and tolerability. Subjects with alopecia totalis, which includes alopecia universalis, will not be allowed in Part A. After completion of the Week 24 efficacy assessments, eligible subjects in Part A will be offered an additional 24 weeks of open-label treatment. To be eligible for an additional 24 weeks of open-label treatment in Part A, subjects must have completed the baseline and Week 24 SALT scores. Also, eligible subjects must have adequate laboratory parameters (must meet entry criteria regarding cytopenias and liver assessments) and, in the opinion of the investigator, have no additional safety concerns related to an additional 24 weeks of open-label treatment.

Part B is double-blind, randomized, and placebo-controlled, with an open-label extension in up to 68 subjects. Initially, 34 subjects will be randomized to INCB018424 1.5% cream or placebo cream, stratified by baseline percentage of scalp involvement with AA (25% to < 50% or 50% to 100%) using the revised Alopecia Areata Investigational Guidelines (rAAIG). Subjects will be treated for 24 weeks to examine efficacy, safety, and tolerability. Subjects with alopecia totalis, which includes alopecia universalis, will be limited to Part B and no more than 10% of the randomized population. Subjects with 25% to < 50% scalp involvement will be limited to no more than 70% of the randomized population in Part B. Part B will complete randomization of an additional 34 subjects if sufficient evidence of terminal hair growth is demonstrated in Part A or the interim analysis of Part B.

Sites will remain blinded to study drug, but some personnel at Incyte without direct contact with sites will be unblinded. An internal committee at Incyte will be charged with evaluating the unblinded interim results based on the futility rule, as well as considering interim safety results.

After the completion of the efficacy assessments for the primary endpoint (Week 24) in the double-blind portion of the study, treatment assignment in Part B will not be unblinded; however, all eligible subjects will be dispensed INCB018424 cream for an additional 24 weeks of open-label treatment. To be eligible for an additional 24 weeks of open-label treatment in Part B, subjects must have completed the baseline and Week 24 SALT scores. Also, eligible subjects must have adequate laboratory parameters (must meet entry criteria regarding cytopenias and liver assessments) and, in the opinion of the investigator, have no additional safety concerns related to an additional 24 weeks of open-label treatment. All areas identified at baseline should continue to be treated through the end of the open-label extension, unless the subject has a complete clinical response.

During the first 24 weeks of treatment in Part A, if new areas of AA develop or existing areas of AA expand after baseline, subjects are NOT to apply study drug to those areas.

In Part B and the open-label extension, if new areas of AA develop or existing areas of AA expand after baseline, subjects are permitted to apply study drug BID to those areas after a visit

to document the SALT score. The visit to document the new or expanded areas may be unscheduled.

After completion of the open-label extension (48 weeks of treatment), subjects who, in the opinion of the investigator, are deriving benefit (some hair regrowth) from INCB018424 will be eligible to enter the long-term extension period for an additional 48 weeks of treatment with open-label INCB018424. Also, eligible subjects must have, in the opinion of the investigator, no additional safety concerns related to an additional 48 weeks of open-label treatment. During the long-term extension period, subjects may stop treating areas that have sufficient regrowth in the opinion of the investigator. Further, after discussion with the investigator, subjects may decrease the application rate to QD in areas with sufficient hair regrowth.

In the open-label extension of Parts A and B or in the long-term extension, subjects who have a complete clinical response (defined as 100% terminal hair regrowth and no evidence of active hair loss) at 2 consecutive visits will stop administration and continue the open-label visits as scheduled. Subjects who have a complete clinical response who subsequently have evidence of hair loss after stopping treatment may restart treatment after a visit to document the SALT score. The visit to document the SALT score may be unscheduled.

Concomitant oral vitamins, shampoos, and hair products should remain stable during the study.

4.2. Measures Taken to Avoid Bias

The study will be double-blind, randomized, and placebo-controlled. An interim analysis will be performed in Part B. Sites will remain blinded to study drug, but some personnel at the sponsor (without direct contact with sites) will be unblinded. Details are provided in Section 9.

4.3. Number of Subjects

Part A will enroll approximately 10 subjects, and Part B will enroll up to approximately 68 subjects. Subjects who discontinue will not be replaced.

4.4. 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 or IEC in writing of the study's completion or early termination, and 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, 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 OF SUBJECTS

5.1. Treatment Groups and Administration of Study Drug

In Parts A and B, study drug will be supplied as INCB018424 1.5% cream or placebo and will be applied topically as a thin film to the affected areas and up to 1 inch (2.5 cm) into the surrounding scalp, where evidence of a decrease in hair density or active loss as evidenced by exclamation point hairs or positive hair pull is present. Study drug should be applied in the morning and in the evening at least 10 hours apart and at least 1 hour before bedtime. All areas identified at baseline should continue to be treated through the end of the open-label extension, unless the subject has a complete clinical response. If there are new areas to be treated (either in the open-label extension of Part A or in Part B), study drug should be applied to these areas in addition to the areas identified at baseline through the end of the open-label extension.

Application instructions will be provided at study visits and via a diary card given to the subjects and are also provided below. At each visit, an estimate of the percentage of scalp surface area to be treated is used to dispense study drug. The prescribed dose is to be determined by weighing a tube before and after the subject applies a thin film of study drug to the affected scalp. For each 10% of scalp surface area to be treated, approximately 1 inch of study drug may be used. Subjects will be advised to limit the use of the cream to ≤ 3.75 grams (1/4 tube) per application or ≤ 1 tube every 2 days.

The subject must be instructed in the handling of study drug as follows:

- Before applying the medicine, wash the area(s) with mild soap or shampoo and water and pat it dry.
- Study drug should be applied topically as a thin film to the affected areas and up to 1 inch (2.5 cm) into the surrounding scalp and rubbed in gently.
- Apply study drug in the morning and in the evening at least 1 hour before bedtime, with applications at least 10 hours apart.
- Wash hands thoroughly with soap and warm water immediately after application of study drug.
- If the study drug is applied by a helper, the helper should wear gloves so they are not exposed to study drug. If exposed, the helper should immediately wash hands thoroughly with soap and warm water.
- Do not cover the application area(s) with a bandage or dressing. If used, occlusive camouflage or other contact should be avoided for at least 1 hour after an application.
- Do not shower afterwards or lie in the sun.
- Do not wash the treatment area(s) for at least 8 hours after application of study drug.
- If topical anti-infectives or other topical treatments are used, these treatments should be avoided for at least 1 hour before and after application of study drug to an area.
- Study drug cream is for dermatological use only and not for ophthalmic use.

- Store the study drug at room temperature.
- Make every effort to take doses on schedule.
- Report any missed doses.
- Keep study drug in a safe place and out of reach of children.
- Bring all used and unused study drug to the site at each visit.

5.1.1. Open-Label Extension Period

In Parts A and B, subjects who have baseline and Week 24 SALT scores will be eligible for an additional 24 weeks of open-label treatment. Eligible subjects must also have adequate laboratory parameters (must meet entry criteria regarding cytopenias and liver assessments) and, in the opinion of the investigator, have no additional safety concerns related to an additional 24 weeks of open-label treatment.

Subjects in Part B who elect to enter the open-label extension will not be unblinded. All eligible subjects will be dispensed INCB018424 cream for the additional 24 weeks of open-label treatment. All areas identified at baseline should continue to be treated through the end of the open-label extension, unless the subject has a complete clinical response.

5.1.2. Long-Term Extension Period

After completion of the open-label extension (48 weeks of treatment), subjects who, in the opinion of the investigator, are deriving benefit (some hair regrowth) from INCB018424 will be eligible to enter the long-term extension period for an additional 48 weeks of treatment with open-label INCB018424. Also, eligible subjects must have, in the opinion of the investigator, no additional safety concerns related to an additional 48 weeks of open-label treatment. During the long-term extension period, subjects may stop treating areas that have sufficient regrowth in the opinion of the investigator. Further, after discussion with the investigator, subjects may decrease the application rate to QD in areas with sufficient hair regrowth.

5.2. Treatment Compliance

Compliance will be assessed by reviewing the subject diaries and by weighing the study drug tubes. Subjects will also be questioned regarding study drug application technique, missing 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 use of the study product. 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 < 80% or > 120% 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 80% but no more than 120% 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.

5.3. Randomization and Blinding

For subjects who have met all study entry criteria and none of the exclusion criteria, contact the IRT at baseline to obtain the study drug assignment.

The study will utilize an IRT for management of study enrollment. In Part A, the IRT will be a simple subject study number assignment and visit tracking configuration, as this is the open-label portion of the study. For Part B, the IRT setup is more complex. The system will assign the subject study number, track subject visits, randomize according to the defined parameters, and maintain the blind. Additionally, the system will employ a configurable stratification algorithm with limits set for the baseline percent scalp involvement (25% to < 50% and 50% to 100%) and alopecia areata type. In Part B, subjects with 25% to < 50% scalp involvement will be limited to no more than 70% of the randomized population, and subjects with alopecia totalis (which includes alopecia universalis) will be limited to no more than 10% of randomized population. If 1 or both of the limits is reached, the IRT will stop assigning randomization numbers to that group, and no additional subjects will be enrolled in that group.

5.4. Duration of Treatment and Subject Participation

After signing the ICF, screening assessments may be completed over a period of up to 28 days in both Part A and Part B. In Part A, screening is up to 28 days; open-label treatment is 24 weeks, with an additional optional 24 weeks of treatment in the open-label extension and an optional 48 weeks of treatment in the long-term extension if eligible; and follow-up is 12 weeks. In Part B, screening is up to 28 days, double-blind treatment is 24 weeks, an optional open-label treatment is 24 weeks in the open-label extension, and an optional 48 weeks of treatment in the long-term extension if eligible, and follow-up is 12 weeks. Total duration of the study is up to 112 weeks in both Part A and Part B.

5.5. Rationale for Dose Modification

Subjects may have new areas emerge during treatment or have existing areas increase in size. Subjects will be allowed to apply additional study drug according to the details in Section 5.6.1.

5.6. Dose Modifications of Study Drug

5.6.1. Planned Dose Modifications

During the first 24 weeks of Part A, if new areas of AA develop or existing areas of AA expand after baseline, subjects are NOT to apply study drug to those areas.

In Part B and in the open-label extension, if new areas of AA develop or existing areas of AA expand after baseline, subjects are permitted to apply study drug BID to those areas after a visit to document the SALT score. All areas identified at baseline should continue to be treated through the end of the open-label extension, unless the subject has a complete clinical response. If there are new areas to be treated (either in the open-label extension of Part A or in Part B), study drug should be applied to these areas in addition to the areas identified at baseline through the end of the open-label extension. The visit to document the new or expanded areas may be unscheduled.

During the long-term extension period, subjects may stop treating areas that have sufficient regrowth in the opinion of the investigator. Further, after discussion with the investigator, subjects may decrease the application rate to QD in areas with sufficient hair regrowth.

In the open-label extension or the long-term extension, subjects with a complete clinical response (defined as 100% terminal hair regrowth and no evidence of active hair loss at 2 consecutive visits, which may include visits during the double-blind period) will stop administration and continue to be followed in the study. Subjects who have a complete clinical response who subsequently have evidence of hair loss after stopping treatment may restart treatment after a visit to document the SALT score.

5.6.2. Criteria and Procedures for Interruption

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) or a Grade 2 decrease in absolute lymphocyte count (< 0.8×10^9/L), ANC (< 1.5×10^9/L), or platelets (< 75×10^9/L). Laboratory abnormalities should be confirmed with repeat testing within 48 hours whenever possible and STAT delivery of the laboratory results requested.
- The subject develops a Grade 3 or higher laboratory abnormality, with the exceptions of lipase (Grade 4, > 5 × ULN) 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 STAT delivery of the laboratory results requested.
- The subject had a Grade 3 or 4 drug-related AE as determined by the investigator.

5.6.3. 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 5.7) during study drug interruption will be withdrawn from the study and may not resume administration.

5.7. Withdrawal of Subjects From the Study

5.7.1. Withdrawal Criteria

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

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

A subject **may** be withdrawn from the study as follows:

- If, during the course of the study, a subject is found not to have met eligibility criteria, 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 opinion of the investigator, the sponsor should be consulted for instruction on handling the subject.

5.7.2. Withdrawal Procedures

In the event that any subject discontinues study drug and, subsequently, withdraws from the study before completion, regardless of reason, reasonable efforts should be made to have the subject return for an early termination visit and have the end-of-treatment (EOT) procedures completed as described in Section 6.4. The date the subject was withdrawn from the study and the specific reason for withdrawal will be recorded in the electronic case report form (eCRF).

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 the follow-up visits. These visits are described in Section 6. The last date of the last dose of study drug will be recorded in the eCRF, and the reason for subject withdrawal will be recorded.

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 or early termination visit should be performed.
- Subjects must be followed for safety until the time of the last follow-up visit or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer.

5.8. Concomitant Medications and Measures

5.8.1. Permitted Medications and Measures

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. Concomitant oral vitamins, shampoos, and hair products ideally should remain stable during the study. All prior medications for AA 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.

5.8.2. Restricted Medications and Measures

- Use of any over-the-counter, nonprescription preparations (including vitamins, minerals, and phytotherapeutic, herbal, or plant derived preparations) within 7 days before the baseline visit, unless deemed acceptable by the investigator.
- Use of any prescription medication (including immunizations, phytotherapeutic, herbal, or plant-derived preparations) within 14 days before the baseline visit, unless deemed acceptable by the investigator.

5.8.3. Prohibited Medications and Measures

The following medications are not permitted during the study:

- Any investigational medication other than the study drugs.
- Other topical agents for AA (including topical minoxidil and topical over-the-counter corticosteroids applied to the scalp), except for stable over-the-counter creams, makeup, and hair colorizers.
- Treatment known to affect the course of AA.
- Systemic minoxidil, corticosteroids, methotrexate, cyclosporine A, and biological therapies, or oral immunosuppressant agents.
- Phototherapy involving ultraviolet light.
- Potent systemic CYP3A4 inhibitors or fluconazole (see Appendix C), until after the last administration of study drug (topical agents with limited systemic availability are permitted).

6. STUDY ASSESSMENTS

All study assessments will be performed as indicated in the schedule of assessments tables. Table 2 presents the assessments for the initial 24 weeks of treatment in Parts A and B. Table 3 presents the assessments for the open-label extension of Part A. Table 4 presents the assessments for the open-label extension of Part B. Table 5 presents the assessments for the long-term extension period. The order of assessments is suggested by the order of mention within the schedule. For instructions on each assessment, see Section 7.

Table 2: Schedule of Assessments for the First 24 Weeks of Treatment in Parts A and B

Evaluation	Section	Screening	Treatment Parts A and B						Follow-Up	
		Day -28 to -1	Day 1	Week 4 Day 29 ± 3 Days	Week 8 Day 56 ± 3 Days	Week 12 Day 84 ± 3 Days	Week 18 Day 126 ± 7 Days	Week 24 EOT Day 168 ± 7 Days	Month 1 ± 7 Days	Month 3 EOS ± 7 Days
Clinic visit		X	X	X	X	X	X	X	X	X
Informed consent	7.1	X								
Contact IRT	7.2	X	X	X	X	X	X	X		
Inclusion/exclusion criteria	3	X	X							
Medical history	7.3	X								
Prior/concomitant meds	7.3.2	X	X	X	X	X	X	X	X	X
Height and body weight	7.3.1	X								
Comprehensive physical exam	7.4.2	X						X		
Targeted physical exam	7.4.3		X	X	X	X	X		X	X
Vital signs	7.4.4	X	X	X	X	X	X	X	X	X
Laboratory assessments	7.4.6	X	X	X	X	X	X	X		X
Hepatitis screening tests	7.4.6.6	X								
Urinalysis	7.4.6.3	X						X		
FSH[a]	7.4.6.4	X								
Pregnancy test[b]	7.4.6.5	X	X	X	X	X	X	X	X	X
12-lead ECG	7.4.5	X						X		
Efficacy assessments	7.5	X	X	X	X	X	X	X	X	X
Hamilton-Norwood Scale[c]								X		
Apply study drug	7.9.1		X	X	X	X	X			
Study drug and diary card dispensed	7.9.4		X	X	X	X	X			
Collect study drug tubes; collect and review diary cards				X	X	X	X	X		
Assess compliance	7.9.3			X	X	X	X	X		
[redacted]										
Photography of scalp	7.5.4		X	X[e]		X		X		X
Assess AEs	7.4.1	X	X	X	X	X	X	X	X	X

FSH = follicle-stimulating hormone.

[a] Serum FSH to be performed for all postmenopausal women only, defined by last menstrual period > 12 months before screening.

[b] All women will have a serum pregnancy test conducted at the screening visit and urine pregnancy tests conducted at all other visits (including baseline).

[c] Assessment of male pattern baldness in male subjects only.

[redacted]

[e] For Part A only: photography of scalp at Week 4.

Table 3: Schedule of Assessments for the Open-Label Extension of Part A

Evaluation	Section	Open-Label Extension Part A					Follow-Up	
		Week 24 Day 168 ± 7 Days	Week 30 Day 210 ± 7 Days	Week 36 Day 252 ± 7 Days	Week 42 Day 294 ± 7 Days	Week 48 EOT Day 336 ± 7 Days	Month 1 ± 7 Days	Month 3 EOS ± 7 Days
Clinic visit			X	X	X	X	X	X
Contact IRT	7.2	X[a]	X	X	X	X		
Prior/concomitant medications	7.3.2		X	X	X	X	X	X
Comprehensive physical exam	7.4.2					X		
Targeted physical exam	7.4.3		X	X	X		X	X
Vital signs	7.4.4		X	X	X	X	X	X
Laboratory assessments	7.4.6		X	X	X	X		X
Urinalysis	7.4.6.3					X		
Pregnancy test[b]	7.4.6.5		X	X	X	X	X	X
12-lead ECG	7.4.5					X		
Efficacy assessments	7.5		X	X	X	X	X	X
Hamilton-Norwood Scale[c]	7.5.5					X		
Apply study drug	7.9.1	X[a]	X	X	X			
Study drug and diary card dispensed	7.9.4	X[a]	X	X	X			
Collect study drug tubes; collect and review diary cards			X	X	X	X		
Assess compliance	7.9.3		X	X	X	X		
Photography of scalp	7.5.4			X		X		X
Assess AEs	7.4.1		X	X	X	X	X	X

EOS = end of study.

[a] All assessments for the Week 24 visit noted in Table 2 as well as these additional activities must be performed before subjects who meet eligibility criteria (see Section 5.1.1) may enter the open-label extension.

[b] Urine pregnancy tests during the open-label extension will be performed on all women.

[c] Assessment of male pattern baldness in male subjects only.

Table 4: Schedule of Assessments for the Open-Label Extension of Part B

Evaluation	Section	Open-Label Extension Part B						Follow-Up	
		Week 24 Day 168 ± 7 Days	Week 28 Day 196 ± 7 Days	Week 32 Day 224 ± 7 Days	Week 36 Day 252 ± 7 Days	Week 42 Day 294 ± 7 Days	Week 48 EOT Day 336 ± 7 Days	Month 1 ± 7 Days	Month 3 EOS ± 7 Days
Clinic visit			X	X	X	X	X	X	X
Contact IRT	7.2	X[a]	X	X	X	X	X		
Prior/concomitant medications	7.3.2		X	X	X	X	X	X	X
Comprehensive physical exam	7.4.2						X		
Targeted physical exam	7.4.3		X	X	X	X		X	X
Vital signs	7.4.4		X	X	X	X	X	X	X
Laboratory assessments	7.4.6		X	X	X	X	X		X
Urinalysis	7.4.6.3						X		
Pregnancy test[b]	7.4.6.5		X	X	X	X	X	X	X
12-lead ECG	7.4.5						X		
Efficacy assessments	7.5		X	X	X	X	X	X	X
Hamilton-Norwood Scale[c]	7.5.5						X		
Apply study drug	7.9.1	X[a]	X	X	X	X			
Study drug and diary card dispensed	7.9.4	X[a]	X	X	X	X			
Collect study drug tubes; collect and review diary cards			X	X	X	X	X		
Assess compliance	7.9.3		X	X	X	X	X		
Photography of scalp	7.5.4				X		X		X
Assess AEs	7.4.1		X	X	X	X	X	X	X

EOS = end of study.

[a] All assessments for the Week 24 visit noted in Table 2 as well as these additional activities must be performed before subjects who meet eligibility criteria (see Section 5.1.1) may enter the open-label extension.

[b] Urine pregnancy tests during the open-label extension will be performed on all women.

[c] Assessment of male pattern baldness in male subjects only.

Table 5: Schedule of Assessments for the Long-Term Extension Period

Evaluation	Section	Week 48 Day 336 ± 7 Days	Week 60 Day 420 ± 7 Days	Week 72 Day 504 ± 7 Days	Week 84 Day 588 ± 7 Days	Week 96 EOT Day 672 ± 7 Days	Follow-Up	
							Month 1 ± 7 Days	Month 3 EOS ± 7 Days
Clinic visit			X	X	X	X	X	X
Contact IRT	7.2	X[a]	X	X	X	X		
Prior/concomitant medications	7.3.2		X	X	X	X	X	X
Comprehensive physical exam	7.4.2					X		
Targeted physical exam	7.4.3		X	X	X		X	X
Vital signs	7.4.4		X	X	X	X	X	X
Laboratory assessments	7.4.6		X	X	X	X		X
Urinalysis	7.4.6.3					X		
Pregnancy test[b]	7.4.6.5		X	X	X	X	X	X
12-lead ECG1	7.4.5					X		
Efficacy assessments	7.5		X	X	X	X	X	X
Hamilton-Norwood Scale[c]	7.5.5					X		
Apply study drug	7.9.1	X[a]	X	X	X			
Study drug and diary card dispensed	7.9.4	X[a]	X	X	X			
Collect study drug tubes; collect and review diary cards			X	X	X	X		
Assess compliance	7.9.3		X	X	X	X		
Photography of scalp	7.5.4		X	X	X	X		X
Assess AEs	7.4.1		X	X	X	X	X	X

EOS = end of study.

[a] All assessments for the Week 48 visit noted in Table 3 or Table 4 (Parts A and B, respectively) as well as these additional activities must be performed before subjects who meet eligibility criteria (see Section 5.1.2) may enter the long-term extension.

[b] Urine pregnancy tests during the long-term extension will be performed on all women.

[c] Assessment of male pattern baldness in male subjects only.

Table 6: Clinical Laboratory Assessments

Serum Chemistries	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 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)

FSH = follicle-stimulating hormone; HCV-RNA = hepatitis C virus ribonucleic acid; IgM = immunoglobulin M.

6.1. Screening

Screening is the interval between the signing of the ICF and the day the subject is enrolled 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 or the 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 if 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 enrolled or randomized in the study.

6.3. Treatment

Subjects who meet all the study entry criteria and none of the exclusion criteria will return to the study site on Day 1 of administration. Dates for subsequent study visits will be determined based on this day and should occur within the visit windows outlined in the schedules of assessments (Table 2, Table 3, Table 4, and Table 5).

The treatment period begins when the subject receives their first dose of study drug, which will be administered in the clinic. At each visit, an estimate of the percentage of scalp surface area to be treated is used to dispense study medication. At each visit, the prescribed dose is to be determined by weighing a tube before and after the subject applies a thin film of study drug to the affected areas and up to 1 inch (2.5 cm) into the surrounding scalp, where evidence of a decrease in hair density or active loss as evidenced by exclamation point hairs or positive hair pull is present. For each 10% of treated scalp, approximately 1 inch of study drug may be used. Tubes of INCB018424 cream or placebo cream will be dispensed to subjects with detailed application instructions.

All subjects in Parts A and B will be treated for 24 weeks. At Week 24, eligible subjects will be offered the opportunity to receive an additional 24 weeks of treatment in the open-label extension. After the completion of the efficacy assessments for the primary endpoint (Week 24) in the double-blind portion of the study, treatment assignment in Part B will not be unblinded; however, all subjects will be dispensed INCB018424 cream for an additional 24 weeks of open-label treatment. All areas identified at baseline should continue to be treated through the end of the open-label extension, unless the subject has a complete clinical response.

For subjects in Part A, any new areas of AA develop or existing areas of AA expand after baseline should not be treated until after Week 24. At any time during treatment for subjects in Part B, and after Week 24 for subjects in Part A, if new areas of AA develop or existing areas of AA expand, subjects are permitted to apply study drug BID to those areas after a visit to document the SALT score. The visit to document the new or expanded areas may be unscheduled.

After completion of the open-label extension (48 weeks of treatment), subjects who, in the opinion of the investigator, are deriving benefit (some hair regrowth) from INCB018424 will be eligible to enter the long-term extension period for an additional 48 weeks of treatment with open-label INCB018424. Also, eligible subjects must have, in the opinion of the investigator, no additional safety concerns related to an additional 48 weeks of open-label treatment. During the long-term extension period, subjects may stop treating areas that have sufficient regrowth in the opinion of the investigator. Further, after discussion with the investigator, subjects may decrease the application rate to QD in areas with sufficient hair regrowth.

In the open-label extension of Parts A and B or in the long-term extension, subjects who have a complete clinical response (defined as 100% terminal hair regrowth and no evidence of active hair loss at 2 consecutive visits, which may include visits at Weeks 18 and 24 in the double-blind portion) will stop administration and continue the open-label visits as scheduled. Subjects who have a complete clinical response who subsequently have evidence of hair loss after stopping treatment may restart treatment after a visit to document the SALT score. The visit to document the SALT score may be unscheduled.

Information regarding a subject's genome will not be collected. Concomitant oral vitamins, shampoos, and hair products should remain stable during the study.

If another person applies study drug, then that person should wear gloves when in contact with study drug.

6.4. End of Treatment

If a decision is made that the subject will permanently discontinue study drug, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, 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.

6.5. Follow-Up Phase

Subjects will have follow-up assessments 1 and 3 months after the last application of study drug or after Week 48 for subjects with a complete clinical response. If prohibited treatment for alopecia is started, an earlier follow-up visit may be performed. A final and thus end-of-study 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 longer. 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.

6.6. 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 AA at an unscheduled visit, then a SALT score and photography should be performed.

6.7. Early Termination

In the event that any subject discontinues the study drug and subsequently the study prior to completion, regardless of reason, reasonable efforts should be made to have the subject return for an early termination visit and have the EOT procedures completed as noted in Table 2.

Subjects who are noncompliant with study drug (defined as < 80% compliant based on tube weight) will have the administration instructions reinforced by the investigator or a qualified designee. After reinforcement, subjects who again fail to meet 80% 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 prior to 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. Subjects of childbearing potential must agree to take appropriate measures to avoid pregnancy in order to participate in the study (Appendix A).

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, IRT will be contacted to obtain study drug assignment. Additionally, IRT will be contacted at each regular study visit to update the study drug supply.

7.3. Demography and History

7.3.1. Demographics and Medical History

Demographic data and a complete medical and medication history will be collected at screening.

7.3.2. Prior and Concomitant Medications

Prior and concomitant medications will be reviewed to determine study eligibility. The medication record will be maintained after enrollment as documentation of concomitant medications, including any changes to the dose or regimen. Concomitant medications include any prescription, over-the-counter, natural, or herbal preparations taken or administered during the study.

7.4. Safety Assessments

7.4.1. 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.

7.4.2. Comprehensive Physical Examination

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.

A comprehensive physical examination will be performed on the days noted in Table 2, Table 3, Table 4, and Table 5. The comprehensive physical examination will include the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; lymph nodes; and a brief neurological examination.

7.4.3. Targeted Physical Examination

A targeted physical examination will be a symptom-directed evaluation and will be performed as necessary on the days noted in Table 2, Table 3, Table 4, and Table 5. The targeted physical examination will include assessments of the body systems or organs, as indicated by subject symptoms, AEs, or other findings as determined by the investigator or designee.

7.4.4. Vital Signs

Vital sign measurements (blood pressure, pulse, respiratory rate, and body temperature) will be taken with the subject in the recumbent, semirecumbent, or sitting position after 5 minutes of rest.

7.4.5. Twelve-Lead Electrocardiograms

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

The 12-lead ECGs will be interpreted by the investigator at the site and will be used for immediate subject management. The decision to include or exclude a subject or withdraw a subject from the study based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate.

7.4.6. Laboratory Assessments

Clinical laboratory tests will be performed using a central laboratory. 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 any additional non-Protocol–required test is performed because of an AE, those results and the normal reference ranges for those analytes must be documented in the eCRF. Otherwise, unscheduled local laboratory test results need not be entered in the eCRF.

Tests required at each visit are shown in Table 2, Table 3, Table 4, and Table 5. 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.

7.4.6.1. Chemistry

A panel of standard serum chemistries will be analyzed at times shown in Table 2, Table 3, Table 4, and Table 5. A list of required analytes is found in Table 6. All serum chemistries will be performed from blood samples collected without respect to food intake (ie, nonfasted).

7.4.6.2. Hematology

Hematology tests will be performed at each study visit indicated in Table 2, Table 3, Table 4, and Table 5. A list of required analytes for scheduled visits is provided in Table 6.

7.4.6.3. Urinalysis

Urinalysis will be performed at each study visit indicated in Table 2, Table 3, Table 4, and Table 5.

7.4.6.4. Fertility Testing

Women who report being amenorrheic for ≥ 1 year will have FSH testing to confirm hormonal menopause; a result of > 30 IU/L will be considered confirmatory. Female subjects thus confirmed as postmenopausal or those who are surgically sterile will be considered to be of nonchildbearing potential.

7.4.6.5. Pregnancy Testing

Pregnancy testing will be performed on all female subjects as noted in the schedules of assessments (Table 2, Table 3, Table 4, and Table 5). 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.

7.4.6.6. Hepatitis Screening Tests

Hepatitis tests shown in Table 6 will be conducted during the screening period. This thorough hepatitis testing is being obtained to better interpret any abnormalities in liver function tests that may develop during the course of the study; therefore, it is not mandatory that results of all tests be available before enrollment (Day 1) if clinical evaluation and medical history provide no reason to suspect ongoing active or subclinical hepatitis infection.

7.5. Efficacy Assessments

7.5.1. Severity of Alopecia Tool Scoring System

Alopecia areata will be assessed using the SALT scoring system recommended by the National Alopecia Areata Foundation group published in the Journal of the American Academy of Dermatology by Olsen et al (2004).

The scalp will be divided into 4 areas (see Appendix B):

- Top of scalp is 40% (0.4) of scalp surface area.
- Right side of scalp is 18% (0.18) of scalp surface area.

- Left side of scalp is 18% (0.18) of scalp surface area.
- Back side of scalp is 24% (0.24) of scalp surface area.

There are 2 acceptable methods of calculating percentage of hair loss in any of these areas:

1. The percentage of hair loss in each area is multiplied by the percentage of surface area of the scalp in that area. The SALT score is the sum of the percentage of hair loss in all of the above mentioned areas. For example, if the percentages of hair loss in the top, right side, left side, and back are 20%, 30%, 40%, and 50%, respectively, the SALT score = $(20 \times 0.4) + (30 \times 0.18) + (40 \times 0.18) + (50 \times 0.24) = 8 + 5.4 + 7.2 + 12 = 32.6$.
2. The SALT score may also be determined directly by assessing the overall hair loss in each section, knowing the percentage covered by each section. For example, the hair loss may be determined to be 8% on the top, 5% on the right side, 7% on the left side, and 12% in the back, or 32% total. Because this method does not use a multiplication factor, the numbers are generally whole.

Whichever method of assessment of the SALT score is used in an individual subject, it should be noted in the source document and used at subsequent visits.

7.5.2. Terminal Hair Regrowth Assessment

At each postbaseline visit, the estimated percentage of any hair regrowth that is terminal pigmented, terminal nonpigmented, or vellus/indeterminate is to be determined. For example, if at baseline there is 50% scalp involvement and at a postbaseline visit there is only 25% scalp involvement, with hair regrowth in 25% of the scalp (a SALT50), and if all of that regrowth is pigmented terminal hair, then it would be recorded as 100% pigmented terminal hair regrowth (since it is 100% of the 25% of the scalp that has hair regrowth).

7.5.3. Physician's Global Assessment of Regrowth

In Part B only, a PGARG score (0, no regrowth; 1, < 25% of regrowth; 2, 25%-49% of regrowth; 3, 50%-74% of regrowth; 4, 75%-99% of regrowth; 5, 100% of regrowth) using live evaluations and referencing baseline photographs will be determined.

7.5.4. Photographs

For each visit with photography, 5 photographs, with views similar to those for the SALT scoring, will be obtained using the Canfield methodology. Photography will be done as follows:

- Part A at baseline and Weeks 4, 12, and 24.
- Part B at baseline and Weeks 12 and 24.
- Open-label extension at Weeks 36 and 48.
- Long-term extension at Weeks 60, 72, 84, and 96.
- Follow-up period at Month 3 (or end-of-study visit).

7.5.5. Hamilton-Norwood Scale

The Hamilton-Norwood Scale is an assessment of male pattern baldness that contains 7 categories (Type I through Type VII; Norwood 1975). Four of the categories have a Type A variant (Type IIa, Type IIIa, Type IVa, and Type Va). Appendix D presents a pictorial representation of the 7 types as well as the 4 variants. Assessment of male pattern baldness will be done by the investigator by examining the subject during the visit in male subjects only at Weeks 24, 48, and 96.

7.6. Performance and Quality of Life Assessments

Not applicable.

[redacted]

7.8. Pharmacodynamic Assessments

Not applicable.

7.9. Other Study Procedures

7.9.1. Administration of Study Drug

INCB018424 cream will be applied as a thin film BID, with applications at least 10 hours apart. The dose strength is 1.5% INCB018424 phosphate (w/w free base equivalent) in a cream

formulation along with the matching placebo cream formulation containing only the vehicle. Application instructions will be provided at study visits and via a diary card given to the subjects. Application instructions will state that the cream is for dermatological use only and not for ophthalmic use. See Section 5.1 for further detail regarding application instructions.

Study drug will be applied in the clinic on the day of a study visit. The prescribed dose is to be determined by weighing a tube before and after the subject applies a thin film of study drug to the affected scalp. For each 10% of affected scalp, approximately 1 inch of study drug may be used. Subjects will be advised to limit the use of the cream to ≤ 3.75 grams (1/4 tube) per application or ≤ 1 tube every 2 days. All areas identified at baseline should continue to be treated through the end of the open-label extension, unless the subject has a complete clinical response.

7.9.2. Dispensing of Study Drug

INCB018424 drug product will be provided as a topical cream, 1.5% (w/w free base equivalent) of INCB018424 phosphate cream and the matching placebo cream will be packaged as 15 grams per tube. Tubes will include labeling "New Drug - Limited by Federal (USA) Law to Investigational Use Only."

At each visit, an estimate of the percentage of scalp surface area to be treated will be used to dispense the number of tubes of study drug.

7.9.3. Assessment of Compliance With Study Drug

Compliance will be assessed by reviewing the subject diaries and by weighing the study drug tubes. Subjects will also be questioned regarding study drug application technique, missing doses, and use of any additional topical or systemic prescriptions of other products or over-the-counter products.

7.9.4. Distribution of Subject Reminder Cards and 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 product. 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 either their study drug (defined as < 80% or > 120% compliant based on prescribed 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 80% but no more than 120% of the expected applications during participation in the treatment phase of the study.

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definitions

For the purposes of this Protocol, an adverse event (AE) is defined as the appearance of or worsening of any pre-existing undesirable sign, symptom, or medical condition 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.

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.

"Disease progression" should not be recorded as an AE itself unless there are no other identifiable AEs associated with the disease progression at the time of reporting. For example, if it is determined that disease progression resulted either in hospitalization, a life-threatening event, or death, then the specific event that led to the subject's hospitalization, life-threatening event, or death should be reported as the AE instead of "disease progression."

Adverse events will be assessed according to the CTCAE v4.03. The CTCAE Grade 5 severity (death) will not be used in this study; rather, AEs with an outcome of death will be reported as CTCAE Grade 4, with an outcome of "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 serious adverse event (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. Concomitant medication or nondrug therapy used to treat an AE should be recorded on the Adverse Event form as well as 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 it, 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, which 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. For analysis purposes, this will be considered 1 AE for this subject and the highest reported severity will be used.

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, and/or per the investigator's discretion. A dose modification for the laboratory abnormality may be required (see Section 5.6.2) 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 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.
  - Any SAEs that are expected due to the condition being treated, including whether the SAE is a primary outcome measure, or where there has been a clear agreement with regulators not to consider these as SAEs, provided the information is collected elsewhere.
- Results in persistent or significant disability or 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 upon 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

To ensure subject safety, every SAE, regardless of suspected causality, occurring after the subject has signed the ICF and up to the last study visit, or up to 30 days after the subject has stopped study treatment, whichever is later, must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence. 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. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported SAE should be reported separately as a new event. Previously planned (ie, before providing informed consent) surgeries

should not be reported as SAEs unless the underlying medical condition worsens over the course of the study.

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

Emergency unblinding for AEs may be performed through IRT, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option may be used ONLY if the subject's well-being requires the investigator to be aware of the subject's treatment assignment. All calls resulting in an unblinding event are recorded and reported by the IRT.

The investigator should make every effort to contact the sponsor's (or its designee's) clinical research physician or medical monitor before unblinding a subject's treatment assignment. If a subject's treatment assignment is unblinded, the sponsor or its designee must be notified immediately by telephone.

If an investigator, site personnel performing assessments, or subject is unblinded, the subject must be withdrawn from the study. In cases where there are ethical reasons to have the subject remain in the study, 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 following in order to ensure subject safety:

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

Data on fetal outcome 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 Investigator's Brochure (IB). Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications (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. 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.

9. STATISTICS

9.1. Study Populations

9.1.1. Part A

All analyses for Part A will be conducted with the Part A evaluable population, which includes all subjects exposed to at least 1 dose of study drug in Part A.

9.1.2. Part B

The intent-to-treat (ITT) population includes randomized subjects who applied at least 1 dose of study drug in Part B. 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 in Part B.

The safety-evaluable population includes all subjects who applied at least 1 dose of study drug in Part B. Treatment groups for this population will be determined by the actual treatment received on Day 1.

[redacted]

9.2. Selection of Sample Size

In Part A, the sample size is based on the demonstration of preliminary findings of hair regrowth. It is anticipated that a sample of 10 subjects will permit sufficient data to decide to enroll more than 34 subjects in Part B (required for the interim analysis).

In Part B, the sample size calculation is based on the Fisher exact test for the primary efficacy endpoint assuming a small expected frequency of responders in the placebo group, given the low response rate. For subjects with 25% to < 50% and 50% to 100% scalp involvement, the response rate is assumed to be 61% for active versus 25% for placebo, and 35% for active versus 5% for placebo, respectively. Using a 2-sided alpha of 0.05 with a continuity correction, 34 subjects per group will have an 80% power to detect a difference between treatment groups.

9.3. Level of Significance

The significance level for efficacy analysis will be 0.05 for 2-sided tests.

9.4. Statistical Analyses

9.4.1. Primary Analyses

In Part A, all efficacy endpoints will be summarized using descriptive statistics in the Part A evaluable population. In Part B, subjects will be stratified at randomization into 2 strata: 25% to < 50% scalp involvement (rAAIG Group S2) and 50% to 100% (rAAIG Groups S3, S4, and S5). The response rate assessed based on SALT50 between active- and placebo-treated subjects will be compared in the ITT population, using a logistic regression with covariates of baseline SALT score and stratification factor of rAAIG group. Exact logistic regression (Mehta and Patel 1995) will be used if any expected numbers are less than 5.

9.4.2. Secondary Analyses

Secondary efficacy analyses will be conducted for the ITT population. Differences in proportions may be compared across treatment groups using similar logistic regression models as specified in the primary analysis. Mean, change from baseline, and percentage change from baseline in quantitative variables will be summarized using descriptive statistics. Mixed models with repeated measures will also be used if appropriate.

9.4.3. Other Analyses

Safety analyses will be conducted for the safety evaluable population. Adverse events will be coded by the MedDRA dictionary, and incidences will be tabulated by preferred term and system organ class for all events, as well as related events. Quantitative safety variables and their changes from baseline (laboratory, vital signs) will be summarized with descriptive statistics. The plasma concentration of INCB018424 data collected at study visits will be analyzed using summary statistics.

Additional supportive endpoints will be summarized. Descriptive statistics with 95% confidence intervals for means or proportions, where appropriate, will also be provided.

9.5. Data Monitoring Committee

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 in Incyte will be charged with evaluating the unblinded interim results based on the futility rule in Section 9.6, as well as considering interim safety results.

9.6. Interim Analysis

9.6.1. Part A

In Part A, the decision to enroll more than 34 subjects in Part B will be mainly based on the number of responders observed or the number of subjects with evidence on other endpoints for hair regrowth. The number of responders that are considered to have sufficient efficacy to complete enrollment of Part B depends on the proportion of subjects enrolled in the stratum for 25% to < 50% scalp involvement and the stratum for 50% to 100% scalp involvement because of the different response rates. For example, if all subjects are enrolled in the 25% to < 50% stratum, using likelihood-based function, applying a binomial distribution, and assuming the null

hypothesis rates of response in the 2 strata, then the probability of observing 5 or more responses in Part A in the 10 subjects is 66%, and so 5 responders will be sufficient to complete enrollment of Part B. If all subjects are in the 50% to 100% stratum, then the probability of observing 2 or more responses is 74%, and so 2 responders will be sufficient to complete enrollment of Part B.

9.6.2. Part B

An interim analysis will be performed when 34 subjects, randomized in Part B, have 12-week data available, and a test for futility will be performed based upon conditional power. The conditional power is the probability to reach significance at the end of the study given the data at the interim. The conditional power will be approximated using the empirical estimates of the treatment effect under the observed trend for a 2-sided alpha of 0.05.

If the conditional power is ≤ 30% and there are more than 10 subjects in each defined stratum, the study will be stopped for futility. If conditional power is ≤ 30% but there is a stratum with ≤ 10 subjects, enrollment of Part B will be continued for that stratum until a total of 20 subjects in that stratum have been randomized in Part B. A second futility analysis will be conducted using the observed difference in SALT50 response rates between the 2 treatment groups in the expanded stratum. If the difference between the 2 observed percentages for the expanded stratum is ≥ 20 percentage points, then randomization will be reopened to the underrepresented stratum until all subjects are randomized in Part B.

Overall, Part B will complete randomization of additional subjects if sufficient evidence of terminal hair growth is demonstrated either at the interim analysis in Part A or at one of the interim analyses in Part B.

An additional interim analysis may be conducted when 24-week data are available for half of the subjects in Part B. The interim analysis will not include any testing for futility or efficacy.

Sites will remain blinded to study drug, but some personnel at Incyte without direct contact with sites will be unblinded. An internal committee in Incyte will be charged with evaluating the unblinded interim results based on the futility rule above, as well as considering interim safety results. If the study is stopped for futility, investigators and subjects will be unblinded, and the decision to continue study drug will be made by the investigator in conjunction with the sponsor, based on an individual assessment of clinical benefit. As there are no plans for stopping early for efficacy, no adjustments of alpha or final p-values for repeated testing are necessary.

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 50, 54, 56, 312, and Part 11; 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.
  - 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 pill or 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 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 Code of Federal Regulations (CFR) Part 54 – Financial Disclosure by Clinical Investigators (ie, "covered studies") are required to submit a completed Clinical Investigator Financial Disclosure form that sufficiently details any financial interests and arrangements that apply. For the purpose of this regulation, "clinical investigator" is defined as any investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects, including the spouse and each dependent child of the clinical investigator or subinvestigator. These requirements apply to both US and foreign clinical investigators conducting covered clinical studies.

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

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.

11. LITERATURE REFERENCES

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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]

[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.

Source: Advisory non-binding guidance from the 15 SEP 2014 Clinical Trial Facilitation Group (CTFG) meeting in Rome.

APPENDIX B. SEVERITY OF ALOPECIA TOOL

Alopecia areata investigational assessment guidelines

SALT scoring system recommended by the National Alopecia Areata Foundation group published in the Journal of the American Academy of Dermatology by Olsen et al (2004) will be used.

The scalp will be divided into 4 areas (see figure below):

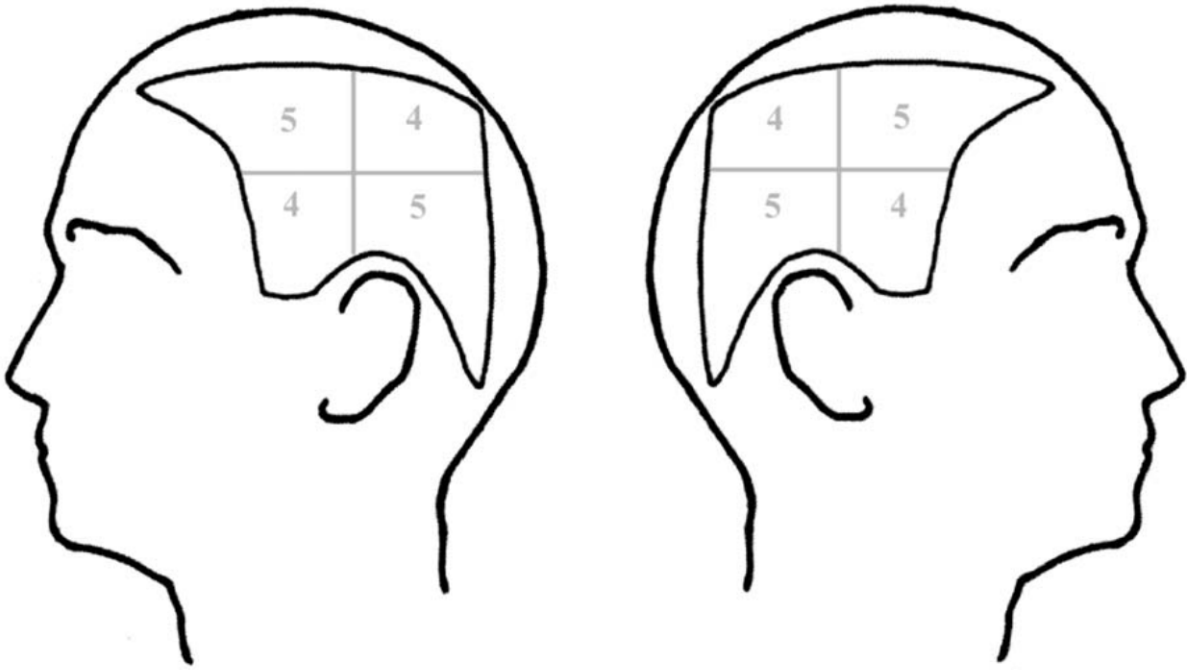
- Top of scalp is 40% (0.4) of scalp surface area.
- Right side of scalp is 18% (0.18) of scalp surface area.
- Left side of scalp is 18% (0.18) of scalp surface area.
- Back side of scalp is 24% (0.24) of scalp surface area.

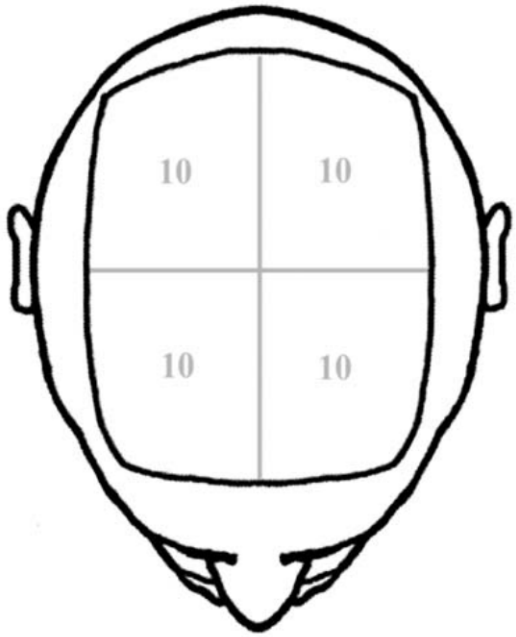
There are 2 acceptable methods of calculating percentage of hair loss in any of these areas:

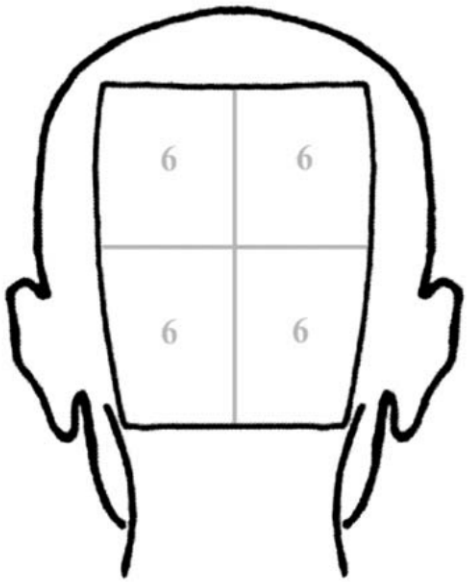
1. The percentage of hair loss in each area is multiplied by the percentage of surface area of the scalp in that area. The SALT score is the sum of the percentage of hair loss in all of the above-mentioned areas. For example, if the percentages of hair loss in the top, right side, left side, and back are 20%, 30%, 40%, and 50%, respectively, the SALT score = $(20 \times 0.4) + (30 \times 0.18) + (40 \times 0.18) + (50 \times 0.24) = 8 + 5.4 + 7.2 + 12 = 32.6$.
2. The SALT score may also be determined directly by assessing the overall hair loss in each section, knowing the percentage covered by each section. For example, the hair loss may be determined to be 8% on the top, 5% on the right side, 7% on the left side, and 12% in the back, or 32% total. Because this method does not use a multiplication factor, the numbers are generally whole.

Whichever method of assessment of the SALT score is used in an individual subject, it should be noted in the source document and used at subsequent visits.

Severity of Alopecia Tool Scoring System Schematic







Olsen/Canfield

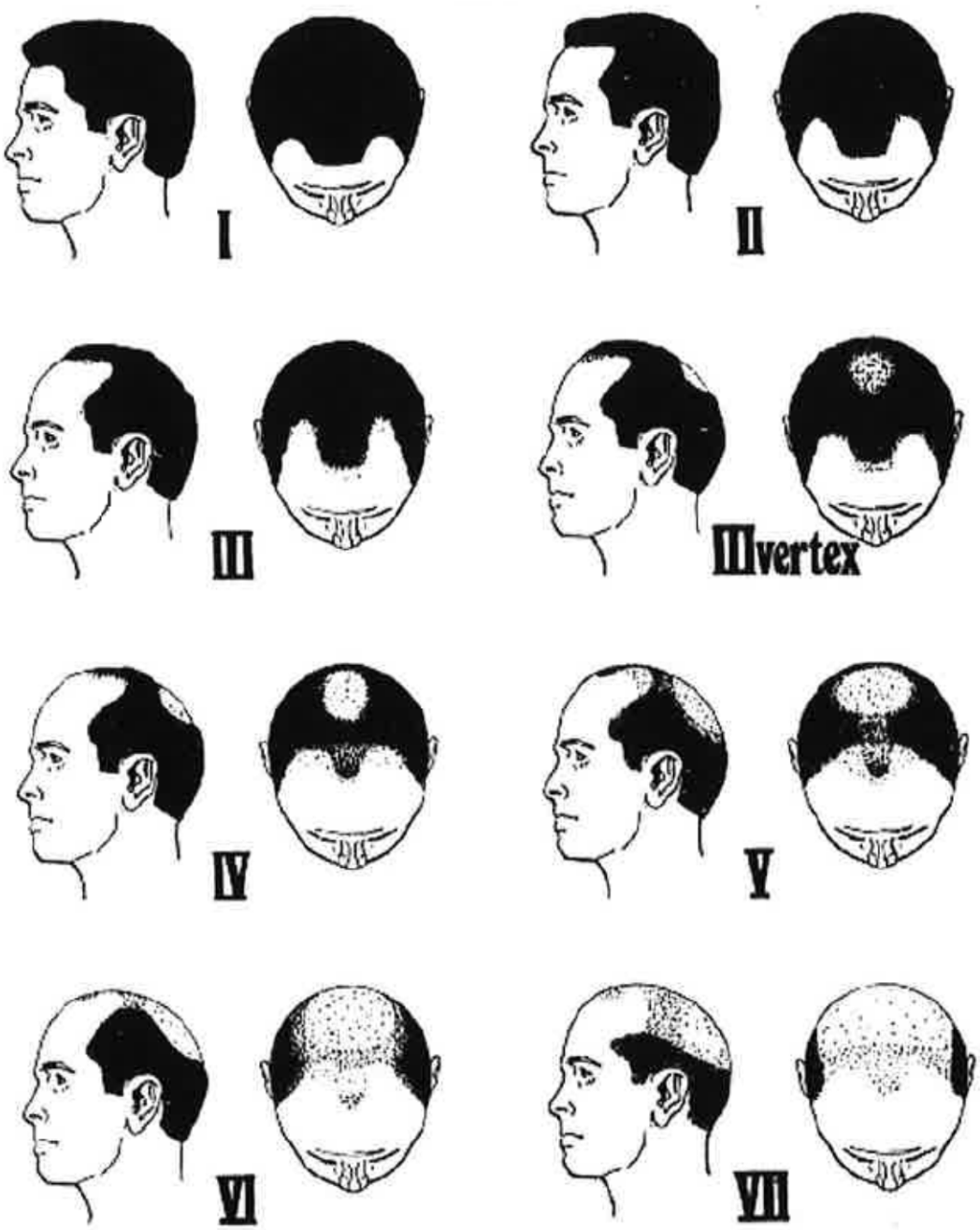
APPENDIX C. POTENT SYSTEMIC CYP3A4 INHIBITORS AND FLUCONAZOLE

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 pharmacokinetic 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 48)); however, topical use of these agents may be permitted on a case-by-case basis if the systemic bioavailability is low. The following is a list of potent systemic CYP 3A4 inhibitors and fluconazole. The sponsor should be contacted with any questions regarding concomitant medications that might be considered potent systemic CYP3A4 inhibitors but are not on this list.

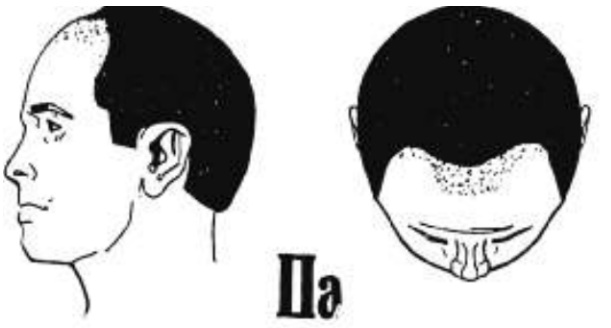
boceprevir
clarithromycin
cobicistat
conivaptan
danoprevir
elvitegravir
fluconazole
grapefruit juice
idelalisib
indinavir
itraconazole
ketoconazole
LCL161
lopinavir
mibefradil
nefazodone
nelfinavir
posaconazole
ritonavir
saquinavir
telaprevir
telithromycin
tipranavir
troleandomycin
voriconazole

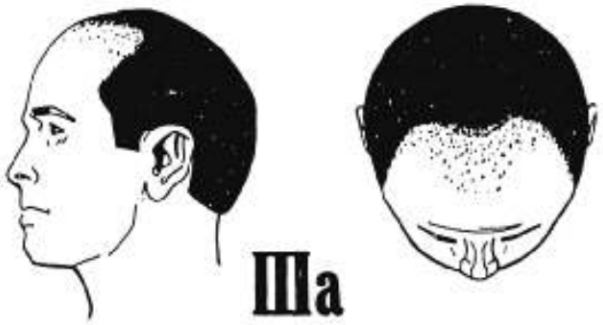
APPENDIX D. HAMILTON-NORWOOD SCALE OF MALE PATTERN BALDNESS

Source: Norwood 1975.



Standards for classification of most common types of male pattern baldness.


IIa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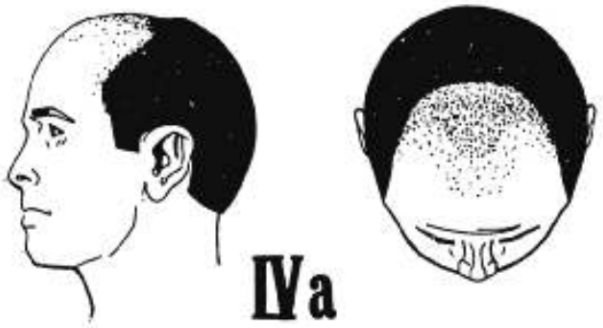
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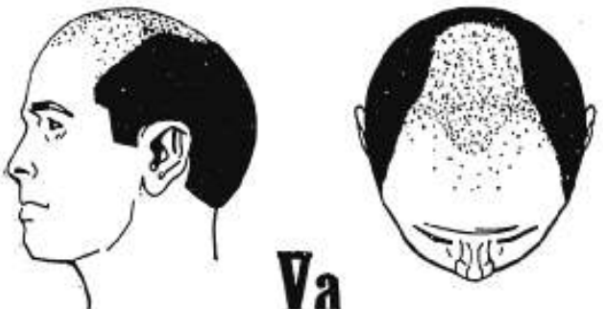
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Document Number: IC-DEV-PROT-AMEND-0192 **Revision:** 0
Title: INCB 18424-204 Protocol Amendment 4

All dates and times are in Eastern Standard Time.

APPROVAL: 18424-204 Amendment 4

Approval and Release

Name/Signature	Title	Date	Meaning/Reason
[redacted]	[redacted]	12 Oct 2016, 11:05:52 AM	Approved
[redacted]	[redacted]	13 Oct 2016, 07:36:51 AM	Approved
[redacted]	[redacted]	13 Oct 2016, 10:57:48 AM	Approved
[redacted]	[redacted]	13 Oct 2016, 11:35:01 AM	Approved

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