Clinical Study Protocol

INCB 18424-206/NCT03011892

A Phase 2, Randomized, Dose-Ranging, Vehicle-Controlled and Triamcinolone 0.1% Cream–Controlled Study to Evaluate the Safety and Efficacy of INCB018424 Phosphate Cream Applied Topically to Adults With Atopic Dermatitis

Product:	**INCB018424 Phosphate Cream**
IND Number:	**77,101**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Date of Protocol:	**15 SEP 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 11, 50, 54, 56, and 312, as well as ICH GCP consolidated guidelines (E6) and applicable regulatory requirements.

INVESTIGATOR'S AGREEMENT

I have read the INCB 18424-206 Protocol (dated 15 SEP 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 Cream	
Title of Study: A Phase 2, Randomized, Dose-Ranging, Vehicle-Controlled and Triamcinolone 0.1% Cream–Controlled Study to Evaluate the Safety and Efficacy of INCB018424 Phosphate Cream Applied Topically to Adults With Atopic Dermatitis	
Protocol Number: INCB 18424-206	**Study Phase:** 2
Indication: Atopic Dermatitis	

Primary Objective:

- To establish the efficacy of each dose of INCB018424 cream once daily (QD) or twice daily (BID) in subjects with atopic dermatitis (AD) compared with vehicle cream BID.

Secondary Objectives:

Key Secondary Objective:

- To establish the efficacy of each dose of INCB018424 cream QD or BID in subjects with AD as compared with triamcinolone 0.1% cream BID.

Other Secondary Objective:

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

[redacted]

Primary Endpoint:

- Mean percentage change from baseline in Eczema Area and Severity Index (EASI) score at Week 4 in subjects treated with 1.5% INCB018424 BID compared with subjects treated with vehicle cream BID.

Secondary Endpoints:

Key Secondary Endpoints:

- Mean percentage change from baseline in EASI score at Week 4 in subjects treated with INCB018424 compared with subjects treated with vehicle cream BID.
- Mean percentage change from baseline in EASI score at Week 4 in subjects treated with INCB018424 compared with subjects treated with triamcinolone 0.1% cream BID.

Other Secondary Endpoints:

- Mean percentage change from baseline in EASI score at Week 2 and Week 8.
- Proportion of subjects who achieve a ≥ 50% improvement from baseline in EASI (EASI-50) at Weeks 2, 4, and 8.
- Assessment of dose response based on percentage change from baseline in EASI score at Week 4.
- Time to achieve EASI-50.

- Proportion of subjects achieving an Investigator's Global Assessment (IGA) score of 0 to 1 who have an improvement of ≥ 2 points from baseline at Weeks 2, 4, and 8.
- Mean change from baseline in the Itch Numerical Rating Scale (NRS) score at Weeks 2, 4, and 8.
- Safety and tolerability assessed by monitoring the frequency, duration, and severity of adverse events (AEs); performing physical examinations; collecting vital signs; and collecting laboratory data for hematology, serum chemistry, and urinalysis.

[redacted]

Overall Study Design:

This is a randomized, vehicle- and active (triamcinolone 0.1% cream)-controlled study in subjects with mild to moderate AD. The study is double-blinded for vehicle, INCB018424 doses, and active control. Approximately 300 subjects will be randomized 1:1:1:1:1:1 to INCB018424 1.5% BID, INCB018424 1.5% QD, INCB018424 0.5% QD, INCB018424 0.15% QD, vehicle BID, and active control (triamcinolone 0.1% cream BID) and stratified by EASI score (≤ 7 and > 7). Subjects receiving QD regimens will apply vehicle at the evening application. Subjects will receive blinded study drug for 8 weeks. Subjects randomized to triamcinolone will apply triamcinolone 0.1% cream BID for 4 weeks and vehicle cream for 4 weeks to not exceed the allowable triamcinolone application duration.

At Week 8, subjects who meet criteria (compliant with the Protocol and no safety concerns) will be offered open-label treatment with INCB018424 1.5% cream BID for 4 weeks.

Through Week 8, subjects should continue to treat areas identified for treatment at baseline even if the area begins to improve. After Week 8, areas which were treated before Week 8 that are no longer symptomatic are not required to be treated.

Subjects will have follow-up assessments 1 month after the last application of study drug.

Study drug (INCB018424 cream, vehicle, or triamcinolone) may not be applied to the face or intertriginous areas. The face and intertriginous areas may be treated with hydrocortisone 2.5% cream during the study. Assessments of BSA should be based on the areas treated with study drug (excluding the face and intertriginous areas that cannot be treated with study drug).

Subjects who develop additional areas of AD after the initiation of treatment may treat these additional

areas (except the face and intertriginous areas) as long as the total treated BSA does not exceed 20% and there are no safety concerns regarding the additional application of study drug.

Subjects may continue to use bland emollients that do not contain urea or ceramides during the study. If bland emollients are used, the type of cream and amount of application should remain consistent for the duration of the study.

An interim analysis will be conducted when at least half of the randomized subjects reach Week 4. These data will be assessed by an unblinded team at the sponsor who does not have direct contact with the study sites.

Sites and the sponsor are blinded to study drug; however, some personnel at Incyte (without direct contact with sites) will be unblinded.

[redacted]

Study Population:

Men or women, aged 18 to 70 years, who have been diagnosed with AD for at least 2 years, with an IGA score of 2 to 3, and BSA involvement (excluding the face and intertriginous areas) of 3% to 20%.

Key Inclusion Criteria:

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

- Adult men and women aged 18 to 70 years, inclusive.
- Subjects diagnosed with AD as defined by the Hanifin and Rajka criteria.
- Subjects with a history of AD for at least 2 years.
- Subjects with an IGA score of 2 to 3 at screening and baseline.
- Subjects with BSA of AD involvement, excluding the face and intertriginous areas, of 3% to 20% at screening and baseline.
- Subjects who agree to discontinue all agents used to treat AD from screening through the final follow-up visit.

Key Exclusion Criteria:

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

- Subjects with evidence of active acute or chronic infections.
- Use of topical treatments for AD (other than bland emollients) within 2 weeks of baseline.
- Systemic immunosuppressive or immunomodulating drugs (eg, oral or injectable corticosteroids, methotrexate, cyclosporine, mycophenolate mofetil, azathioprine) within 4 weeks or 5 half-lives of baseline (whichever is longer).
- Subjects with other dermatologic disease besides AD whose presence or treatments could complicate the assessment of disease (eg, psoriasis).
- Subjects with a history of other diseases besides dermatologic disorders (eg, other autoimmune diseases) taking treatments that could complicate assessments.
- Subjects with cytopenias at screening, defined as:
  - Leukocytes $< 3.0 \times 10^9$/L.
  - Neutrophils < lower limit of normal.
  - Hemoglobin < 10 g/dL.
  - Lymphocytes $< 0.8 \times 10^9$/L.
  - Platelets $< 100 \times 10^9$/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.
- Subjects taking potent systemic cytochrome P450 3A4 inhibitors or fluconazole within 2 weeks or 5 half-lives, whichever is longer, before the baseline visit (topical agents with limited systemic availability are permitted).
- Subjects who have previously received Janus kinase inhibitors, systemic or topical (eg, ruxolitinib, tofacitinib, baricitinib, filgotinib, lestaurtinib, pacritinib).

INCB018424 Cream/Study Drug, Dosage, and Mode of Administration:

INCB018424 1.5% cream, INCB018424 0.5% cream, and INCB018424 0.15% cream will be supplied and applied topically as a thin film to the affected areas in the morning and in the evening at least 1 hour before bedtime. The prescribed dose of study drug is to be determined by weighing a tube before and after the subject applies a thin film of study drug to the affected areas. For each 1% of BSA (palm with fingers) to be treated with study drug, approximately 2 inches (5 cm) of study drug may be used. Subjects will be advised to limit use to no more than 1 tube per application. Application instructions will be provided at study visits and via a diary card given to the subjects. If sunscreen, makeup, or other cream has been applied to the areas to be treated, subjects should wash the treatment areas with mild soap and water and pat dry before application of study drug. If used, topical anti-infectives or other topical treatments should be avoided for at least 1 hour before and after application of study drug to an area. Subjects should be cautioned to avoid excessive exposure to either natural or artificial sunlight (including tanning booths, sun lamps, etc) and, when outdoors, should be advised to wear loose-fitting clothing that protects the treated area from the sun. Immediately after application of study drug, subjects are to wash hands thoroughly with soap and warm water.

Reference Therapy, Dosage, and Mode of Administration:

Vehicle cream is matching in appearance to the INCB018424 creams, except it does not contain active drug. Vehicle cream and triamcinolone 0.1% cream are to be applied in the same manner as INCB018424 cream. Triamcinolone 0.1% cream treatment of 4 weeks will be followed by vehicle treatment for 4 weeks. Subjects receiving QD regimens of INCB018424 cream will receive vehicle cream at the evening application.

Study Schedule/Procedures:

Study visits as follows:

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

Treatment: Subjects will have study visits on Day 1 and at Weeks 2, 4, 8, 10, and 12 for assessment of safety and efficacy.

Study drug will be applied in the clinic on the day of a study visit. Subjects will be given a daily diary to record application times. Subjects will also be instructed to bring all study drug tubes with them to each visit so that compliance can be assessed.

Safety follow-up: Subjects will have follow-up assessments 30 (± 7) days after the last dose of study drug to assess safety and efficacy. If prohibited treatment for AD is started, then an earlier follow-up visit will be performed as a final, and thus end-of-study, visit.

Safety assessments:

At each scheduled study visits at the clinical site, targeted physical examinations, vital sign collection, laboratory assessments, collection of concomitant medications, and AE assessments will be performed. A 12-lead ECG will be performed at screening. All laboratory assessments will be performed using a

central laboratory except for urine pregnancy tests. Toxicities will be monitored continuously and will be graded using the National Cancer Institute CTCAE v4.03 criteria.

Efficacy assessments:

The EASI score, [redacted], IGA, [redacted] will be assessed at all visits (screening; Day 1; Weeks 2, 4, 8, 10, and 12; and the follow-up visit).

Photographs of the areas of AD [redacted] will be conducted on Day 1 and at Week 4.

[redacted]

The Itch NRS will be assessed daily using an electronic diary.

[redacted]

Estimated Duration of Participation:

The total duration of participation will be up to 20 weeks, including up to 4 weeks for screening, 8 weeks of double-blind treatment, 4 weeks of open-label treatment, and 4 weeks of safety follow-up.

Estimated Number of Subjects: Approximately 300 subjects will be enrolled in the study at up to 75 study centers.

Principal Coordinating Investigator: [redacted], MD/MTR, [redacted] USA

Statistical Methods:

The sample size was calculated based on the power analysis and control of Type I error. For the primary and key secondary analyses, comparisons between each active treatment group and vehicle or active control based on mean percentage change from baseline in EASI will be performed for the intent-to-treat population with a fixed-effect ANOVA model. To control the family-wise error rate (2-sided, 0.05), a graphic approach based on the weighted Bonferroni will be used. All secondary [redacted] efficacy measures will be evaluated using descriptive statistics. The clinical safety data (vital signs, routine laboratory tests, and AEs) will be analyzed using descriptive statistics.

An interim analysis will be conducted when at least half of the randomized subjects reach Week 4. These data will be assessed by an unblinded team at the sponsor who does not have direct contact with the study sites.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

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

Term	Explanation
AA	alopecia areata
AC	active control
AD	atopic dermatitis
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
AST	aspartate aminotransferase
BID	twice daily
BSA	body surface area
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximal plasma concentration
COMFORT	Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
EASI	Eczema Area and Severity Index
EASI-50	≥ 50% improvement in EASI score
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
H	head
HCV-RNA	hepatitis C virus ribonucleic acid
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IGA	Investigator's Global Assessment

Term	Explanation
IgM	immunoglobulin M
IL	interleukin
IN	Investigator Notification
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
JAK	Janus kinase
LL	lower limbs
MedDRA	Medical Dictionary for Regulatory Activities
ni.	noninferiority
NOAEL	no-observed-adverse-effect level
NRS	Numerical Rating Scale
PK	pharmacokinetic
PV	polycythemia vera
QD	once daily
RA	rheumatoid arthritis
RNA	ribonucleic acid
[redacted]	[redacted]
s.	superiority
SAE	serious adverse event
STAT	signal transducers and activators of transcription
SUSAR	suspected unexpected serious adverse reaction
T	trunk
TSH	thyroid-stimulating hormone
UL	upper limbs
ULN	upper limit of normal
V	vehicle

1. INTRODUCTION

INCB018424 cream is a topical formulation of INCB018424 phosphate under development for the treatment of subjects with psoriasis, alopecia areata (AA), and atopic dermatitis (AD). 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, AA, and AD. Because JAKs serve to translate extracellular signals from a number of relevant cytokines and growth factors upregulated in inflammatory diseases such as psoriasis, AA, and AD, JAK inhibitors represent potential therapeutic agents for these disease states.

1.1. Atopic Dermatitis

Atopic dermatitis affects approximately 20% of children and 10% of adults (Silverberg and Hanifin 2013), is increasing in incidence, and costs $3.8 billion a year in direct medical costs alone (Ellis et al 2002). Although not life-threatening, patients with AD are at higher risk for the development of other life-threatening disorders such as asthma and food allergy (Spergel 2010). Furthermore, according to the recent Global Burden of Disease project, worldwide AD is one of the 50 most prevalent diseases, and it has the second highest disability rank of all nonmalignant skin diseases (Hay et al 2014). Strikingly, despite the advances in targeted biologic treatments for psoriasis, no targeted therapies currently exist for AD.

Topical therapies are limited to topical steroids, which have associated side effects from long-term use, including glucocorticoid-induced folliculitis and localized skin atrophy. The use of systemic glucocorticoids is also limited because of the adverse event (AE) profile. If current topical therapies fail, then systemic immunosuppressive agents (eg, cyclosporine, methotrexate) are occasionally employed with highly variable efficacy and/or high risk of AEs. However, recent studies indicate that oral JAK inhibitors are effective in the treatment of AD (Levy et al 2015). New approaches that improve AD symptoms and quality of life without introducing safety issues are urgently needed.

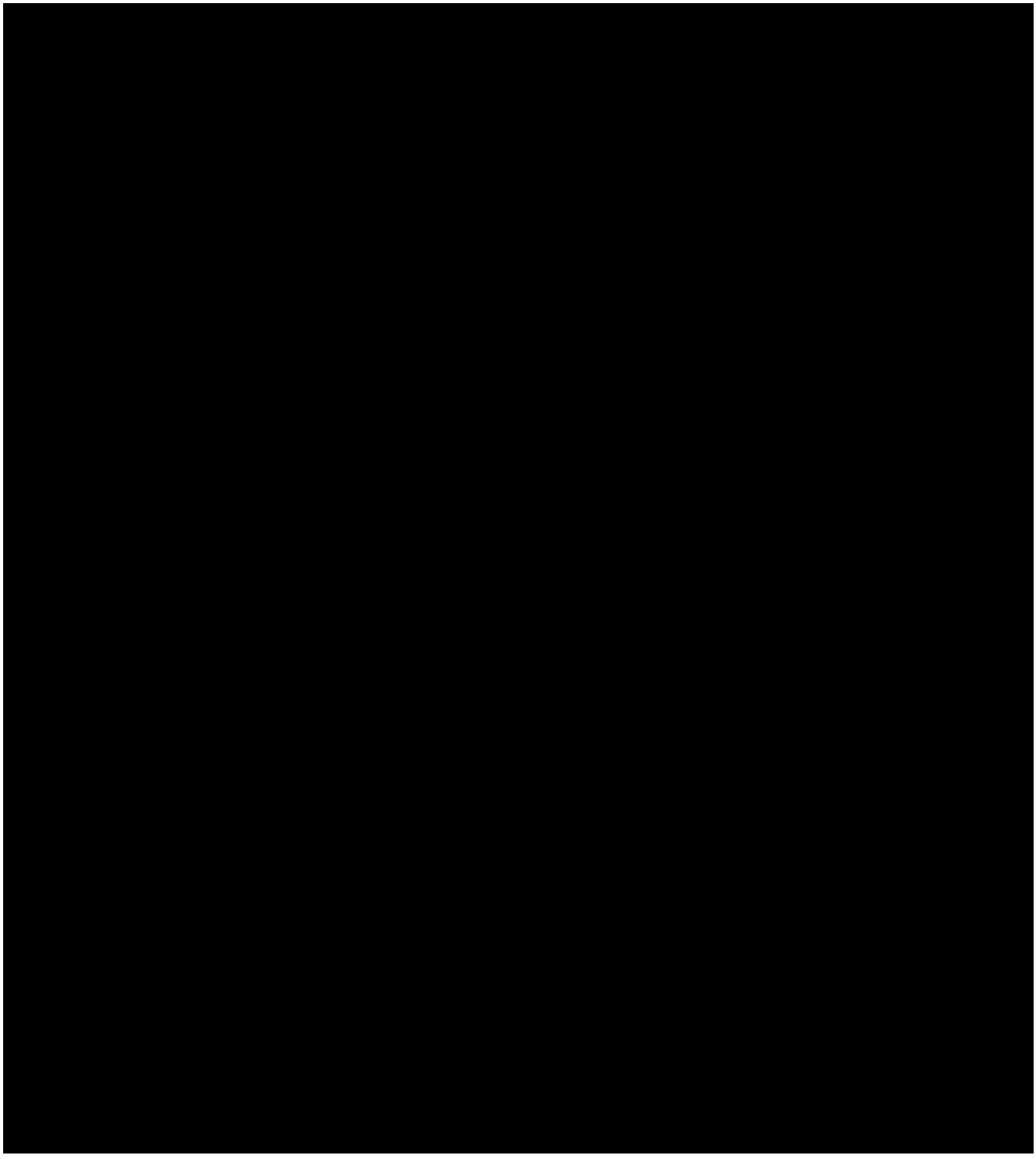
1.2. Inflammation and Atopic Dermatitis

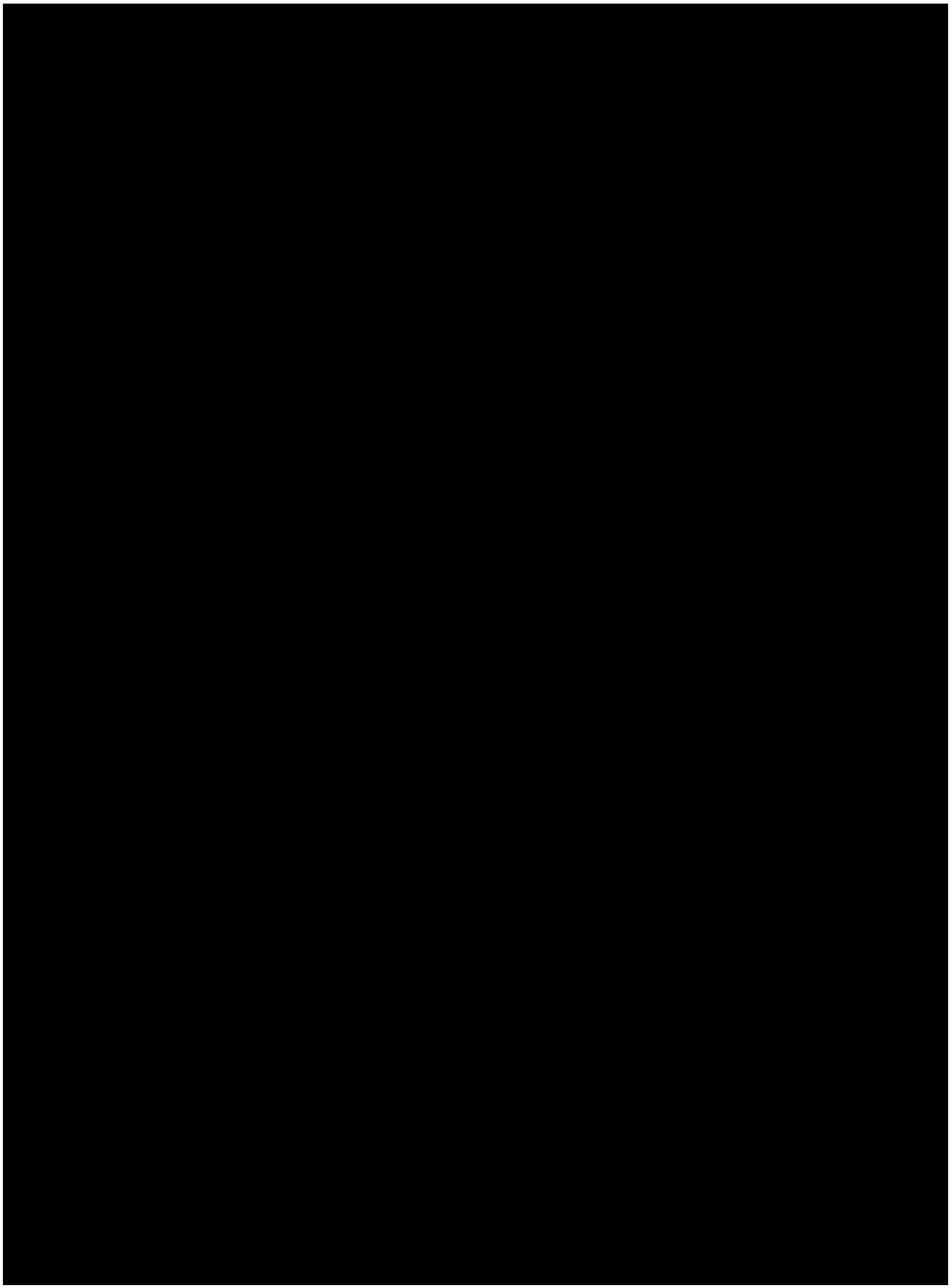
Type 2 inflammation is widely known to underlie the pathogenesis of AD. A number of studies have highlighted that T helper type 2 cells, group 2 innate lymphoid cells, and basophils, which all produce the type 2 cytokines interleukin (IL)-4, IL-5, and/or IL-13, are highly pathogenic in the setting of AD (Kim 2015). Indeed, all of these cells are increased in frequency in lesional skin from AD patients. Further blockade of these type 2 cytokines decreases disease in both murine models and in patients (Kim et al 2014, Beck et al 2014). Taken together, simultaneous disruption of multiple type 2 inflammatory cytokine–associated pathways via JAK inhibition may serve as a novel therapeutic modality in AD.

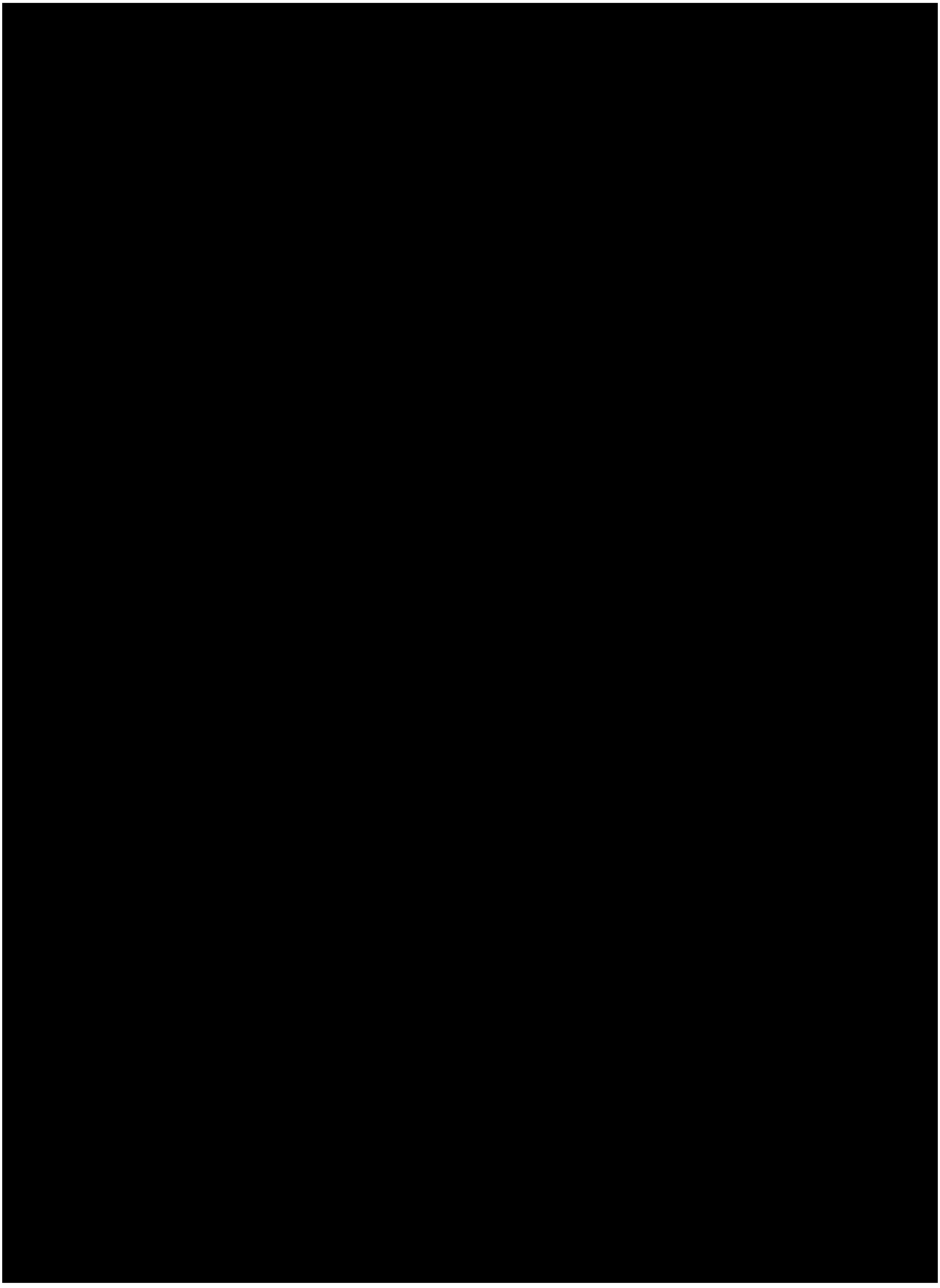
1.3. Role of Janus Kinases in Atopic Dermatitis

The type 2 cytokines IL-4 and IL-13 signaling through JAK1. A number of drugs in clinical studies for AD are designed to block these cytokines and are highly promising new biologic agents (eg, dupilumab and lebrikizumab; Beck et al 2014). However, these new drugs employ humanized monoclonal antibody-mediated approaches, which cannot be used topically. Thus,

topical JAK1 inhibition presents a unique approach to develop a novel nonsteroidal anti-inflammatory agent. Studies with oral tofacitinib (JAK1- and JAK3-inhibitor) have already demonstrated efficacy in AD. Thus, topical treatment with INCB018424 phosphate is a highly promising approach for the treatment of AD. To date, a topical JAK inhibitor with sufficient skin penetration has not yet been approved in AD. 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 subjects with psoriasis.







[redacted]

1.7. Clinical Experience

1.7.1. Clinical Efficacy With Topical INCB018424 in Psoriasis

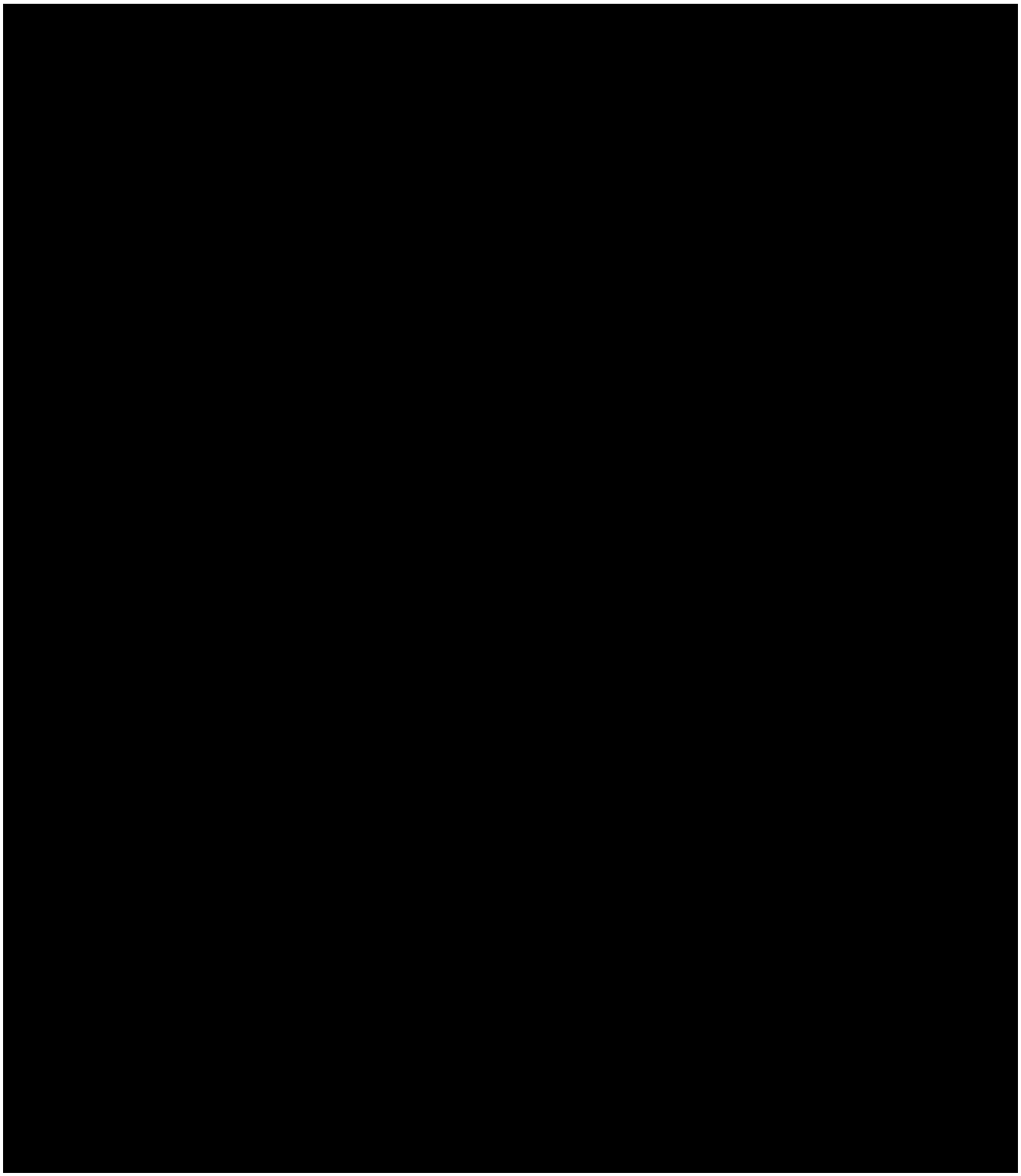
In a double-blind, vehicle- or comparator-controlled, ascending dose, safety, tolerability, PK, and preliminary efficacy study of INCB018424 cream in subjects with plaque psoriasis (Study INCB 18424-201), efficacy was demonstrated with both the 1% cream applied QD and the 1.5% cream applied BID, with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

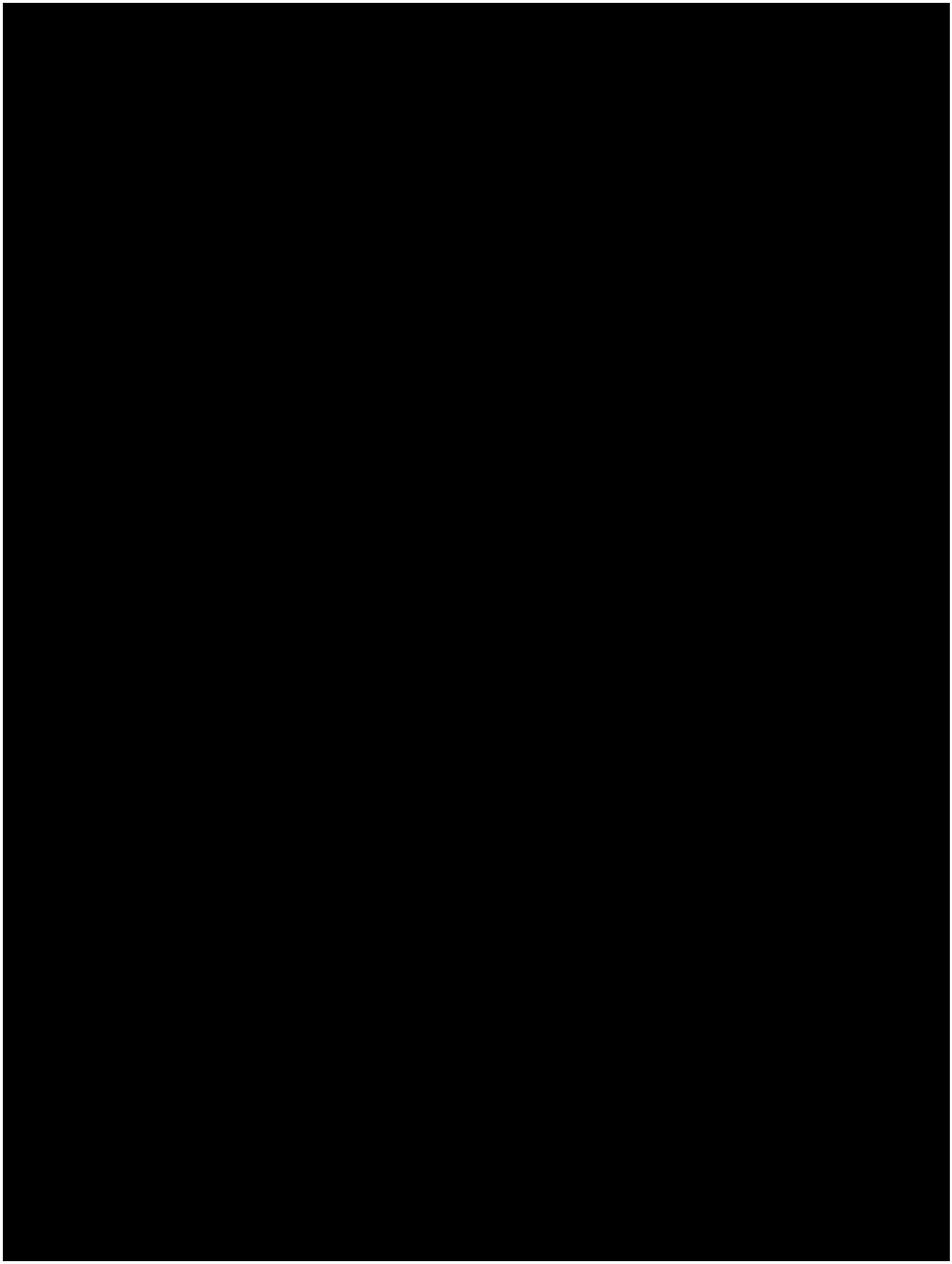
In an open-label, multicenter, sequential-cohort, dose-escalation, safety, tolerability, PK, pharmacodynamic, and preliminary efficacy study of INCB018424 1% or 1.5% cream applied to 2% to 20% BSA QD or BID for 4 weeks in subjects with active, stable plaque psoriasis (Study INCB 18424-202), the efficacy 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.

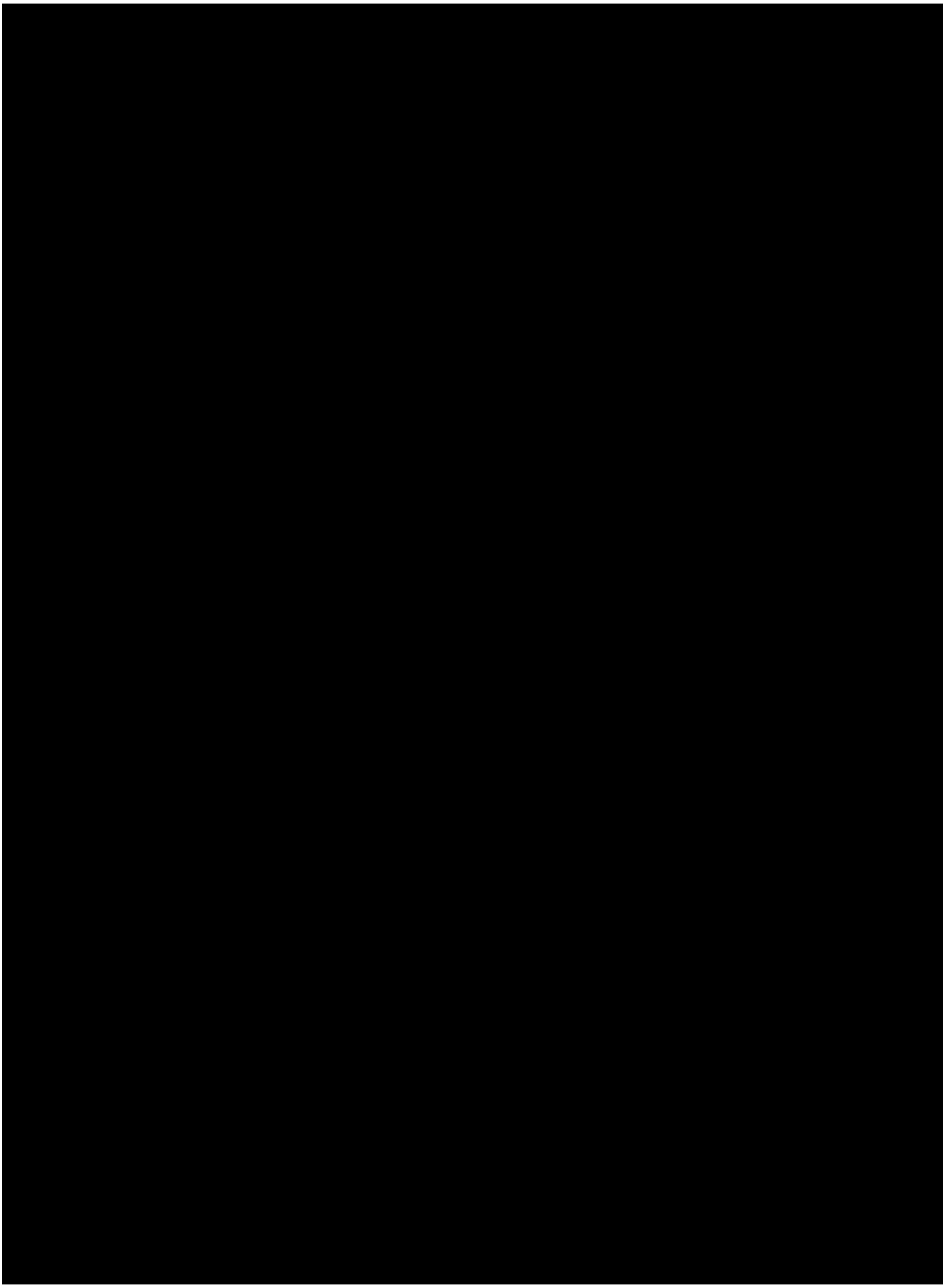
Study INCB 18424-203 was a 12-week, randomized, multicenter, parallel-group, vehicle-controlled, double-blind, dose-ranging study designed to evaluate the safety and efficacy of QD application of INCB018424 cream (0.5%, 1.0%, or 1.5%) relative to vehicle cream in subjects with stable plaque psoriasis. Within each active treatment group, the mean scores for the individual and total psoriasis lesion assessments, the Psoriasis Area Severity Index, the Physician Global Assessment, and the mean treatable percentage of 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.

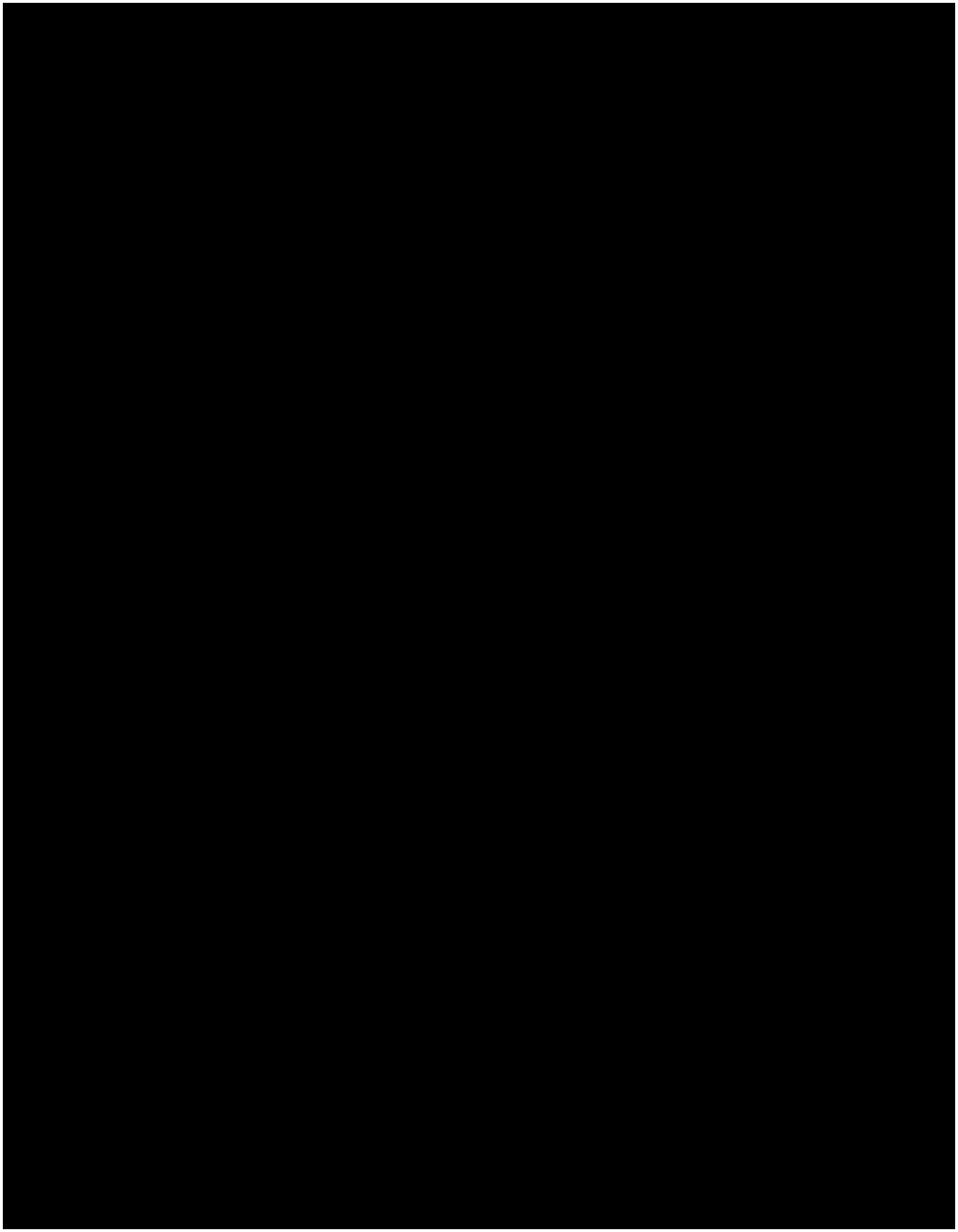
1.7.2. Clinical Experience With JAK Inhibition in Atopic Dermatitis

Topical tofacitinib 2% BID was studies in a Phase 2 randomized vehicle-controlled clinical study in subjects with mild to moderate AD. Over a 4-week period, improvements were noted in disease activity (Eczema Area and Severity Index [EASI] and patient-reported pruritus) and it was generally safe and well-tolerated (Poulin et al 2015).









[redacted]

1.7.5. Oral INCB018424 (Ruxolitinib) Safety

In the randomized period of the 2 pivotal studies in myelofibrosis, Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment (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%).

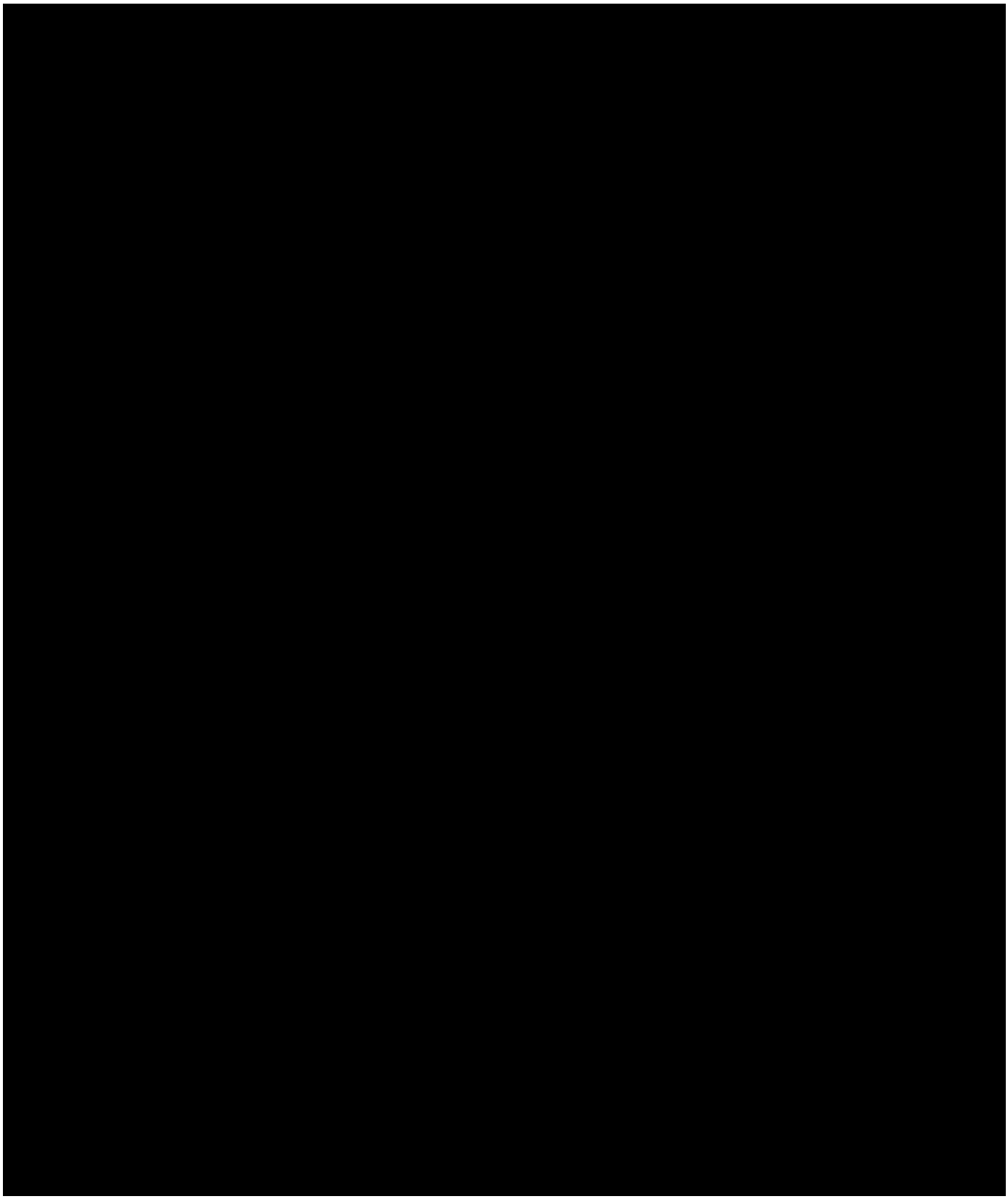
Long-term follow-up in subjects with myelofibrosis (including 615 subjects treated with ruxolitinib during the controlled and extension phases of Studies INCB 18424-251 cutoff 01 OCT 2012, COMFORT-I cutoff 02 SEP 2012, and COMFORT-II cutoff 01 SEP 2012 has shown that, as expected, the numbers and proportions 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 rheumatoid arthritis (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.



2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

- To establish the efficacy of each dose of INCB018424 QD or BID in subjects with AD compared with vehicle cream BID.

2.1.2. Secondary Objectives

2.1.2.1. Key Secondary Objective

- To establish the efficacy of each dose of INCB018424 cream QD or BID in subjects with AD as compared with triamcinolone 0.1% cream BID.

2.1.2.2. Other Secondary Objective

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

[redacted]

2.2. Study Endpoints

2.2.1. Primary Endpoint

- Mean percentage change from baseline in EASI score at Week 4 in subjects treated with 1.5% INCB018424 BID compared with subjects treated with vehicle cream BID.

2.2.2. Secondary Endpoints

2.2.2.1. Key Secondary Endpoints

- Mean percentage change from baseline in EASI score at Week 4 in subjects treated with INCB018424 compared with subjects treated with vehicle cream BID.
- Mean percentage change from baseline in EASI score at Week 4 in subjects treated with INCB018424 compared with subjects treated with triamcinolone 0.1% cream BID.

2.2.2.2. Other Secondary Endpoints

- Mean percentage change from baseline in EASI score at Week 2 and Week 8.
- Proportion of subjects who achieve a ≥ 50% improvement from baseline in EASI (EASI-50) at Weeks 2, 4, and 8.
- Assessment of dose response based on percentage change from baseline in EASI score at Week 4.
- Time to achieve EASI-50.
- Proportion of subjects achieving an Investigator's Global Assessment (IGA) score of 0 to 1 who have an improvement of ≥ 2 points from baseline at Weeks 2, 4, and 8.
- Mean change from baseline in the Itch Numerical Rating Scale (NRS) score at Weeks 2, 4, and 8.
- 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. Adult men and women aged 18 to 70 years, inclusive.
2. Subjects diagnosed with AD as defined by the Hanifin and Rajka (1980) criteria.
3. Subjects with a history of AD for at least 2 years.
4. Subjects with an IGA score of 2 to 3 at screening and baseline.
5. Subjects with BSA of AD involvement, excluding the face and intertriginous areas, of 3% to 20% at screening and baseline.
6. Subjects who agree to discontinue all agents used to treat AD from screening through the final follow-up visit.

7. Willingness to avoid pregnancy or fathering of 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.
8. 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. Subjects with evidence of acute acute or chronic infections.
2. Use of topical treatments for AD (other than bland emollients) within 2 weeks of baseline.
3. Systemic immunosuppressive or immunomodulating drugs (eg, oral or injectable corticosteroids, methotrexate, cyclosporine, mycophenolate mofetil, azathioprine) within 4 weeks or 5 half-lives of baseline (whichever is longer).
4. Subjects with other dermatologic disease besides AD whose presence or treatments could complicate the assessment of disease (eg, psoriasis).
5. Subjects with a history of other diseases besides dermatologic disorders (eg, other autoimmune diseases) taking treatments that could complicate assessments.
6. Subjects with cytopenias at screening, defined as:
    a. Leukocytes $< 3.0 \times 10^9$/L.
    b. Neutrophils < lower limit of normal.
    c. Hemoglobin < 10 g/dL.
    d. Lymphocytes $< 0.8 \times 10^9$/L.
    e. Platelets $< 100 \times 10^9$/L.
7. 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).

8. Subjects taking potent systemic CYP3A4 inhibitors or fluconazole within 2 weeks or 5 half-lives, whichever is longer, before the baseline visit (topical agents with limited systemic availability are permitted, see Appendix C).
9. Subjects who have previously received JAK inhibitors, systemic or topical (eg, ruxolitinib, tofacitinib, baricitinib, filgotinib, lestaurtinib, pacritinib).
10. Women who were pregnant or breastfeeding within 4 months before screening.
11. Current or recent history (< 30 days before screening and/or < 45 days before randomization) of a clinically meaningful bacterial, fungal, parasitic, or mycobacterial infection.
12. 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 or human immunodeficiency virus (HIV) antibody.
13. Current clinically meaningful viral infection (eg, eczema herpeticum).
14. Clinically significant or uncontrolled cardiac disease, including unstable angina, acute myocardial infarction within 6 months from Day 1 of study drug administration, New York Heart Association Class III or IV congestive heart failure, and arrhythmia requiring therapy or uncontrolled hypertension (blood pressure > 150/90 mmHg) unless approved by medical monitor/sponsor.
15. 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.
16. 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.
17. Use of any prohibited medications (see Section 5.6.3) within 14 days or 5 half-lives (whichever is longer) of the baseline visit.
18. 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.
19. Receipt of blood products within 2 months before screening.
20. Subjects with a history of malignancy, except for the following adequately treated, nonmetastatic malignancies: basal cell skin cancer not involving the lesions being treated with study medication, squamous cell carcinomas of the skin not involving the lesions being treated with study medication, or *in situ* cervical cancer.
21. Subjects who anticipate receiving a live or live-attenuated vaccination from screening through the final follow-up visit.
22. 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 randomized, vehicle- and active (triamcinolone 0.1% cream)-controlled study in subjects with mild to moderate AD. The study is double-blinded for vehicle, INCB018424 doses, and active control. Approximately 300 subjects will be randomized 1:1:1:1:1:1 to INCB018424 1.5% BID, INCB018424 1.5% QD, INCB018424 0.5% QD, INCB018424 0.15% QD, vehicle BID, and active control (triamcinolone 0.1% cream BID) and stratified by EASI score (≤ 7 and > 7). Subjects receiving QD regimens will apply vehicle at the evening application. Subjects will receive blinded study drug for 8 weeks. Subjects randomized to QD regimens will apply vehicle for the evening application. Subjects randomized to triamcinolone will apply triamcinolone 0.1% cream BID for 4 weeks and vehicle cream for 4 weeks to not exceed the allowable triamcinolone application duration (Figure 2).

At Week 8, subjects who meet criteria (compliant with the Protocol and no safety concerns) will be offered open-label treatment with INCB018424 1.5% cream BID for 4 weeks.

Through Week 8, subjects should continue to treat areas identified for treatment at baseline even if the area begins to improve. After Week 8, areas which were treated before Week 8 that are no longer symptomatic are not required to be treated.

Subjects will have follow-up assessments 1 month after the last application of study drug.

Study drug (INCB018424 cream, vehicle, or triamcinolone) may not be applied to the face or intertriginous areas. The face and intertriginous areas may be treated with hydrocortisone 2.5% cream during the study. Assessments of BSA should be based on treated areas (excluding the face and intertriginous areas that cannot be treated with study drug).

Subjects who develop additional areas of AD after the initiation of treatment may treat these additional areas (except the face and intertriginous areas) as long as the total treated BSA does not exceed 20% and there are no safety concerns regarding the additional application of study drug.

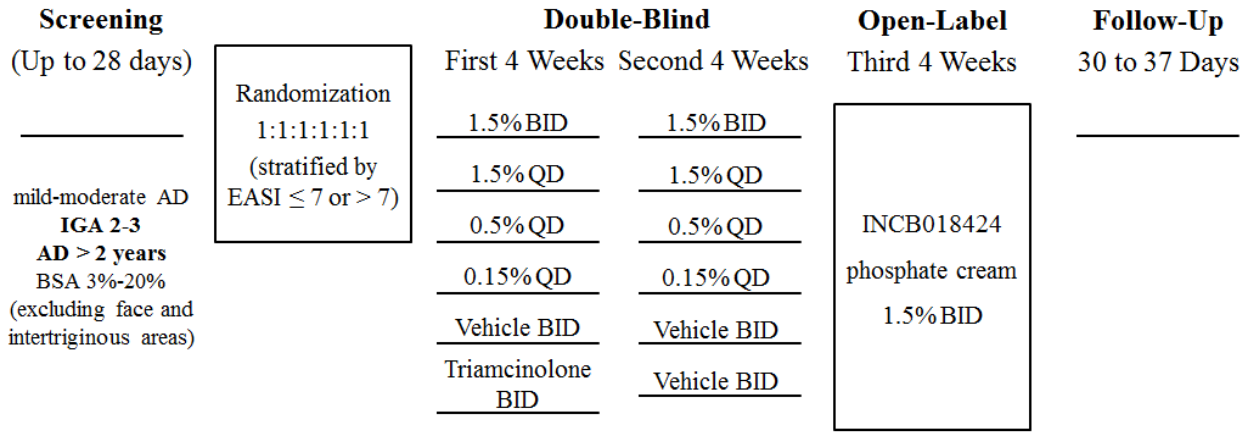
Subjects may continue to use bland emollients that do not contain urea or ceramides during the study. If bland emollients are used, the type of cream and amount of application should remain consistent for the duration of the study.

An interim analysis will be conducted when at least half of the randomized subjects reach Week 4. These data will be assessed by an unblinded team at the sponsor who does not have direct contact with the study sites.

Sites and the sponsor are blinded to study drug; however, some personnel at Incyte (without direct contact with sites) will be unblinded.

[redacted]

Figure 2: Study Design



QD regimens will apply vehicle in the evening.
Subjects may apply 2.5% hydrocortisone cream to the face and intertriginous areas.

4.2. Measures Taken to Avoid Bias

The study is randomized and double-blinded with a vehicle and active comparator (triamcinolone 0.1% cream). A designated site staff member will be assigned to dispense and collect study drug, as well as instruct and assist with application of study drug during the clinic visits. This person should not have study responsibilities that involve either efficacy or safety assessments. Returned study drug should be collected before other study assessments being performed. Study drug should be dispensed at the end of the visit by the same designated staff, after other visit assessments have been completed. When the study drug is dispensed at the study visit, the morning dose of study drug for that visit should be applied. The subject should be counseled at this time regarding questions about dose or method of application.

4.3. Number of Subjects

The study will randomize approximately 300 subjects in a ratio of 1:1:1:1:1:1. Subjects who discontinue will not be replaced.

4.4. Duration of Treatment and Subject Participation

The total duration of participation will be up to 20 weeks, including up to 4 weeks for screening, 8 weeks of double-blind treatment, 4 weeks of optional open-label treatment, and 4 weeks of safety follow-up.

4.5. Overall Study Duration

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

4.6. Study Termination

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

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

5. TREATMENT

5.1. Treatment Assignment

5.1.1. Subject Numbering and Treatment Assignment

All subject numbers will be 6 digits; the first 3 digits will be the site number, and the last 3 digits will be the subject's number. This subject number will be maintained throughout the study and will not be reassigned. Subjects who withdraw consent or discontinue from the study after being assigned a subject number will retain their initial number.

The study will utilize an interactive response technology (IRT) for management of study enrollment. The system will assign the subject study number, track subject visits, randomize according to the defined parameters, track study drug, and maintain the blind. Site staff will contact the IRT after screening is completed to enroll the subject and to allocate the subject to treatment assignment and obtain the initial study drug assignment. The investigator or designee will select the appropriate kit from their stock that corresponds to the information provided by the IRT and dispense the study drug to the subject. All subsequent dispensing of study drug should follow this process. Full details will be provided in the IRT manual.

5.1.2. Randomization and Blinding

For subjects who have met all study inclusion criteria and none of the exclusion criteria, the IRT should be contacted at baseline to obtain the study drug assignment.

The IRT system will set minimum entry criteria for an IGA score of 2 or 3, a BSA 3% to 20%, and will stratify the treatment groups based on baseline EASI score of ≤ 7 and > 7. If 1 or both of the limits are reached, the IRT will stop assigning randomization numbers to that group, and no additional subjects will be enrolled in that group. Subjects, investigators, and the sponsor will remain blinded to each subject's treatment assignment throughout the study (with the exception of the unblinded team that will assess the results of interim analysis). Emergency unblinding will occur if an AE requires the investigator to be made aware of the subject's treatment assignment (see emergency unblinding procedures in Section 8.4 and refer to the Study Reference Manual).

5.2. INCB018424 Cream, Matching Vehicle, or Active Comparator

5.2.1. Description and Administration

INCB018424 1.5% cream, INCB018424 0.5% cream, INCB018424 0.15% cream, vehicle cream, or triamcinolone acetonide 0.1% cream will be applied topically as a thin film to the affected areas (except the face and intertriginous areas) in the morning and in the evening at least 1 hour before bedtime, with applications at least 8 hours apart. 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. If sunscreen, makeup, or other cream has been applied to the areas to be treated, subjects should wash the treatment areas with mild soap and water and pat dry before application of study drug. If used, topical anti-infectives or other topical treatments should be avoided for at least 1 hour before and after application of study drug to an area. Subjects should be cautioned to avoid excessive exposure to either natural or artificial sunlight (including tanning booths, sun lamps, etc) and, when outdoors, should be advised to wear loose-fitting clothing that protects the treated area from the sun as well as apply sunscreen (see Section 5.6.1 for permitted sunscreens). Immediately after application of study drug, subjects are to wash hands thoroughly with soap and warm water.

Vehicle cream is matching in appearance to the INCB018424 creams, except that it does not contain active drug. Subjects receiving QD regimens of INCB018424 cream will receive vehicle cream at the evening application. Triamcinolone acetonide 0.1% cream is in a different vehicle. Vehicle cream and triamcinolone 0.1% cream are to be applied in the same manner as INCB018424 cream.

The prescribed dose of study drug is to be determined by weighing a tube before and after the subject applies a thin film of study drug to the affected areas. For each 1% of BSA (palm with fingers) to be treated with study drug, approximately 2 inches (5 cm) of study drug may be used. Subjects will be advised to apply cream as a thin film to the affected areas and limit use to no more than 1 tube per application.

For all study visits where applicable, study drug should be applied at the visit to verify proper dispensing and application by the subject.

5.2.2. Supply, Packaging, and Labeling

INCB018424 drug product will be provided as INCB018424 1.5%, 0.5%, and 0.15% cream, or vehicle 1.5% (w/w free base equivalent) of INCB018424 phosphate cream. INCB018424 cream (all doses), INCB018424 vehicle cream, and triamcinolone 0.1% cream and will be packaged as 15 grams per tube. Tubes will include labeling for morning or evening application.

Tubes will include labeling in the local language and will comply with the legal requirements of each country.

5.2.3. Storage

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

5.3. Treatment Compliance

Compliance will be assessed for frequency of administration and total amount of application of study drug 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 drug. The completed diary will be collected during each visit. Qualified clinical staff will review the subjects' entries for compliance. Subjects who are noncompliant with study drug (defined as < 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 portion 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.

5.4. Treatment Interruptions and Adjustments

5.4.1. Dose Modifications

Subjects who have additional areas of AD develop after the initiation of treatment may treat these additional areas (except the face and intertriginous areas) as long as the total treated BSA does not exceed 20%, amount of study drug applied does not exceed 1 tube per application, and there are no safety concerns regarding the additional application of study drug. After Week 8, areas that were treated before Week 8 that are no longer symptomatic are not required to be treated.

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

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

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

- The subject develops a Grade 2 increase in ALT (> 3 × ULN) or AST (> 3 × ULN), or a Grade 2 decrease in ANC (< 1.5×10^9/L) or platelets (< 75×10^9/L), or a Grade 3 decrease in absolute lymphocyte count (< 0.5×10^9/L). Laboratory abnormalities should be confirmed with repeat testing within 48 hours whenever possible and STAT delivery of the laboratory results requested.
- The subject develops a Grade 3 or higher laboratory abnormality, with the exceptions of lipase (in which case a Grade 4, > 5 × ULN, results in discontinuation of study medication) or any asymptomatic triglyceride, cholesterol, or amylase elevations. Laboratory abnormalities should be confirmed with repeat testing within a medically indicated timeframe, based upon the investigator's judgment and in collaboration with the sponsor's medical monitor, and STAT delivery of the laboratory results requested.
- The subject had a Grade 3 or 4 drug-related AE as determined by the investigator.

5.4.3. Criteria for Permanent Discontinuation of Study Drug

Subjects who have administration interrupted based on above criteria will be followed until the parameters return to the normal range or to baseline values. Laboratory evaluations can be repeated as frequently as daily. A subject who has had their dose interrupted based on these criteria may resume administration with study drug at a later time if the subject no longer meets the criteria for interrupting the dose with the sponsor's approval in consultation with the

investigator. Subjects who meet withdrawal criteria (see Section 5.5.1) during study drug interruption will be withdrawn from the study and may not resume administration.

5.5. Withdrawal of Subjects From Study Treatment

5.5.1. Withdrawal Criteria

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

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

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

- If, during the course of the study, a subject is found not to have met eligibility criteria, then the medical monitor, in collaboration with the investigator, will determine whether the subject should be withdrawn from the study.
- Subjects who are noncompliant with study drug (defined as < 80% or > 120% 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% or > 120% 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 of the subject before withdrawal.
- If a subject is noncompliant with study procedures in the investigator's opinion, the sponsor should be consulted for instruction on handling the subject.

5.5.2. Withdrawal Procedures

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

If a subject is withdrawn from the study:

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal must be documented in the subject's medical record and in the eCRF.
- The EOT visit should be performed.

- The date of the EOT visit should be recorded in the IRT.
- Subjects must be followed for safety until the time of the follow-up visit or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

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

5.6. Concomitant Medications

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

6. STUDY ASSESSMENTS

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

Table 2: Schedule of Assessments

Evaluation	Protocol Section	Screening	Treatment						EOT	Follow-Up
		Day -28 to -1	Baseline Day 1	Week 2 Day 14 ± 3 Days	Week 4 Day 28 ± 3 Days	Week 8 Day 56 ± 7 Days	Week 10 Day 70 ± 3 Days	Week 12 Day 84 ± 7 Days		30 ± 7 Days After Last Dose
Administrative procedures										
Informed consent	7.1	X								
Contact IRT	7.2	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	3	X	X							
Demography and medical history	7.3	X								
Prior/concomitant medications	7.4	X	X	X	X	X	X	X	X	X
Dispense study drug and diary card	7.10.1		X	X	X	X	X			
Apply study drug	5.2		X	X	X	X	X			
Collect study drug tubes and review diary cards	7.10.1			X	X	X	X	X	X	
Assess compliance	5.3			X	X	X	X	X	X	
Safety procedures/assessments										
Comprehensive physical examination (height and weight at screening only)	7.5.2.1	X								X
Targeted physical examination	7.5.2.2		X	X	X	X	X	X	X	X
Vital signs	7.5.3	X	X	X	X	X	X	X	X	X
Hematology and chemistry assessments	7.5.5	X	X	X	X	X	X	X	X	
Free T4 and thyroid stimulating hormone		X								
Urinalysis	7.5.5.3	X								
Pregnancy test[a]	7.5.5.4	X	X	X	X	X	X	X	X	X
Serology	7.5.5.5	X								
12-lead ECG	7.5.4	X								
Assess AEs	7.5.1	X	X	X	X	X	X	X	X	X
Efficacy assessments										
EASI scoring	7.6.1	X	X	X	X	X	X	X	X	X
BSA treated w/study drug (4 regions and overall)	7.6.5	X	X	X	X	X	X	X	X	X
[redacted]										
IGA	7.6.2	X	X	X	X	X	X	X	X	X
Photography	7.6.6		X		X					
[redacted]										
Itch Numerical Rating Scale	7.6.4	Diary is completed each evening from screening through the last dose of study drug.								
[redacted]										

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

[redacted]

Table 3: 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 Urine pregnancy test (at site) Serum pregnancy test Free T4 TSH	Hepatitis B surface antigen Hepatitis B core antibody Hepatitis B core IgM antibody Hepatitis C virus antibody HCV-RNA (only performed if antibody positive) HIV antibody

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

6.1. Screening

Screening is the interval between the signing of the ICF and the day that 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 whether the subject continues to meet the eligibility requirements as specified in the Protocol.

Subjects who have signed the ICF and meet all the entry criteria (see Section 3) may be enrolled or randomized in the study on Day 1.

6.3. Treatment

Subjects who meet all of the study inclusion 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 schedule of assessments (Table 2).

The treatment period begins when the subject receives their first dose of study drug, which will be administered in the clinic. The amount of study medication to be obtained from the pharmacy is determined by the BSA to be treated. On Day 1, 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. For each 1% of BSA (palm with fingers) to be treated with study drug, approximately 2 inches (5 cm) of study drug may be used. Subjects will be advised to limit use to no more than 1 tube per application. Tubes of INCB018424 cream, triamcinolone 0.1% cream, or vehicle cream will be dispensed to subjects with detailed application instructions. The face and intertriginous areas may be treated with hydrocortisone 2.5% cream throughout the study.

For all study visits, subjects should apply the morning dose of study drug in the clinic to assess understanding of dispensing and application. A designated site staff member will be assigned to dispense and collect study drug, as well as instruct and assist with application of study drug during the clinic visits. This person should not have study responsibilities that involve either efficacy or safety assessments. Returned study drug should be collected before other study assessments being performed. Study drug should be dispensed at the end of the visit by the same designated staff, after other visit assessments have been completed. The subject should be counseled at this time regarding questions about dose or method of application.

Subjects who are noncompliant with study drug (defined as < 80% or > 120% 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% or > 120% 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 of the subject before withdrawal.

6.4. End of Treatment/Early Termination

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

6.5. Follow-Up

After the EOT visit (Weeks 8 or 12, or early termination), subjects will have follow-up assessments 1 month later to monitor for durability of effect (relapse rate), AEs, medication history, vital signs, and clinical assessments. If prohibited treatment for AD 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. If needed, a follow-up phone call will be conducted to determine any AEs or SAEs during the 30 days after the last dose of study drug. Reasonable efforts should be made to have the subject return for the follow-up visit and report any AEs that may occur during follow-up.

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 the subject develops new areas of AD, treatment of the new areas may begin after documenting of the new EASI score and photography of the new or expanding areas. This may occur at an unscheduled visit.

7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

7.1. Administration of Informed Consent Form

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

7.2. Interactive Response Technology Procedure

The IRT will be contacted to obtain a subject ID number when a subject enters screening. Upon determining that the subject is eligible for study entry, the IRT will be contacted to obtain the treatment assignment. Additionally, the IRT will be contacted at each regular study visit to update the study drug supply. Full details will be provided in the IRT manual.

7.3. Demography and Medical History

7.3.1. Demographics and General Medical History

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

7.3.2. Disease Characteristics and Treatment History

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

7.4. Prior and Concomitant Medications and Procedures

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

7.5. Safety Assessments

7.5.1. Adverse Events

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

7.5.2. Physical Examinations

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

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

7.5.2.1. Comprehensive Physical Examination

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

7.5.2.2. Targeted Physical Examination

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

7.5.3. Vital Signs

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

7.5.4. Electrocardiograms

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

The 12-lead ECGs will be interpreted by the investigator at the site to 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. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

7.5.5. 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 if those results lead to a dose modification, delay, or dose interruption, or if any additional non-Protocol–required test is performed because of an AE, then those results and the normal reference ranges for those analytes must be documented in the eCRF. Otherwise, unscheduled local laboratory test results need not be entered in the eCRF.

Additional analytes may be requested based on emerging data, if indicated for safety of study subjects. In addition, some subjects may receive additional assessments as medically indicated; results of nonrequired tests may also be entered in the eCRF.

7.5.5.1. Chemistry

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

7.5.5.2. Hematology

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

7.5.5.3. Urinalysis

Urinalysis will be performed at screening indicated in Table 2.

7.5.5.4. Pregnancy Testing

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

7.5.5.5. Serology

Subjects will be tested for hepatitis and HIV as shown in Table 3. Serology 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.

7.6. Efficacy Assessments

7.6.1. Eczema Area and Severity Index Score

Atopic dermatitis will be assessed using the EASI scoring system (Appendix B), which is a validated disease measurement for clinical studies (Hanifin et al 2001). The severity strata for the EASI are as follows: 0 = clear; 0.1 to 1.0 = almost clear; 1.1 to 7.0 = mild; 7.1 to 21.0 = moderate; 21.1 to 50.0 = severe; 50.1 to 72.0 = very severe (Leshem et al 2015).

7.6.2. Investigator's Global Assessment

The grades for the IGA are shown in Table 4.

Table 4: Investigator's Global Assessment

Grade	Severity	Status
0	Clear	No inflammatory signs of AD
1	Almost clear	Just perceptible erythema and just perceptible papulation/infiltration
2	Mild disease	Mild erythema and mild papulation/infiltration
3	Moderate disease	Moderate erythema and moderate papulation/infiltration
4	Severe disease	Severe erythema and severe papulation/infiltration
5	Very severe disease	Severe erythema and severe papulation/infiltration with oozing/crusting

7.6.4. Itch Numerical Rating Scale

The Itch NRS is a daily patient-reported measure (24-hour recall) of itch intensity. Subjects will be asked to rate the itching severity because of their AD by selecting a number from 0 (no itch) to 10 (worst imaginable itch) that best describes their worst level of itching in the past 24 hours.

Subjects will be issued a hand-held device (eDiary) on which to record itch severity. The subject will be instructed to complete the eDiary each night beginning on the day of screening through treatment discontinuation. Subjects will bring the device to the study site at each study visit so that the device charging can be verified and accumulated data can be downloaded, as applicable. The device will then be returned to the subject for continued use each night. The subject will return the device and the docking station for the final time at the EOT visit so that the data can be archived. Detailed directions for the administration of the eDiary will be provided in the Study Reference Manual.

[redacted]

7.6.6. Photography

For each visit with photography (baseline and Week 4), photographs of the areas of AD [redacted] will be obtained.

[redacted]

7.10. Other Study Procedures

7.10.1. Distribution of Subject Diaries

Starting at the Day 1 visit and each visit thereafter, a diary will be given to each subject in order to record use of the study 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 AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related, that occurs after a subject provides informed consent. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically meaningful, require therapy (eg, hematologic abnormality that requires transfusion), or require changes in the study drug(s).

8.1.2. Reporting

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

The severity of AEs will be assessed using CTCAE v4.03 Grades 1 through 4. The CTCAE v4.03 severity of Grade 5 will not be used; AEs resulting in death will be graded accordingly using Grades 1 through 4 and have the outcome noted as fatal. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity:

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

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

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

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

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

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

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

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

8.2. Laboratory Test Abnormalities

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

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

8.3. Serious Adverse Events

8.3.1. Definitions

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

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

8.3.2. Reporting

Every SAE, regardless of suspected causality (eg, relationship to study drug(s) or study procedure or disease progression), occurring after the subject has signed the ICF through the last study visit (or 30 days after the last dose of study drug, whichever is later) must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence, unless otherwise specified by the Protocol. Any SAEs occurring more than 30 days after the last dose of study drug should be reported to the sponsor or its designee only if the investigator suspects a causal relationship to the study drug.

Information about all SAEs is collected and recorded on the Adverse Event form of the eCRF. The investigator must assess and record the causal relationship of each SAE to the study treatment.

The investigator must also complete the Incyte Serious Adverse Event Report Form, in English, and send the completed and signed form to the sponsor or designee within 24 hours of becoming aware of the SAE. The investigator must provide a causality assessment, that is, assess whether there is at least a reasonable possibility that the SAE is related to the study treatment: suspected

(yes) or not suspected (no). Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.

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

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

If the SAE is not documented in the IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, the sponsor or its designee may urgently require further information from the investigator for reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

8.4. Emergency Unblinding of Treatment Assignment

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

The investigator 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; however, this is not mandatory. 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 treatment. 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 followed in order to ensure subject safety:

- The study drug must be discontinued immediately (female subjects only; see Section 5.4 for the maximum permitted duration of study drug interruption).
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

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

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

8.6. Warnings and Precautions

Special warnings or precautions for the study drug, derived from safety information collected by the sponsor or its designee, are presented in the 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. Data Monitoring Committee

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

8.8. Product Complaints

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

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

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

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

9. STATISTICS

9.1. Study Populations

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

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

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

[redacted]

9.2. Selection of Sample Size

The assumptions in Table 5 were used for the percentage change from baseline in EASI scores at Week 4.

Table 5: Assumed Percentage Change From Baseline in EASI at Week 4

Treatment	Percentage Change
Vehicle	30%
Triamcinolone 0.1% (active control)	50%
INCB018424 1.5% BID	75%
INCB018424 1.5% QD	65%
INCB018424 0.5% QD	50%
INCB018424 0.15% QD	30%

The standard deviation was assumed to be 0.13 (13%). These assumptions were based on the review of a historical clinical study in AD (Beck et al 2014).

In order to provide a large safety database and to provided adequate power for efficacy variables, the total sample size for the study is 300 subjects randomized in a 1:1:1:1:1:1 ratio (stratified by baseline EASI score) to INCB018424 1.5% BID, INCB018424 1.5% QD, INCB018424 0.5% QD, INCB018424 0.15% QD, triamcinolone (active control), and vehicle.

9.2.1. Graphical Procedure

A graphical procedure with gatekeeping testing strategy for the primary and key secondary analyses will be implemented. A family of 7 elementary hypotheses, corresponding to treatment comparison between each active dose group to vehicle or triamcinolone is evaluated in Figure 3 based on the percentage change from baseline to Week 4 of EASI score.

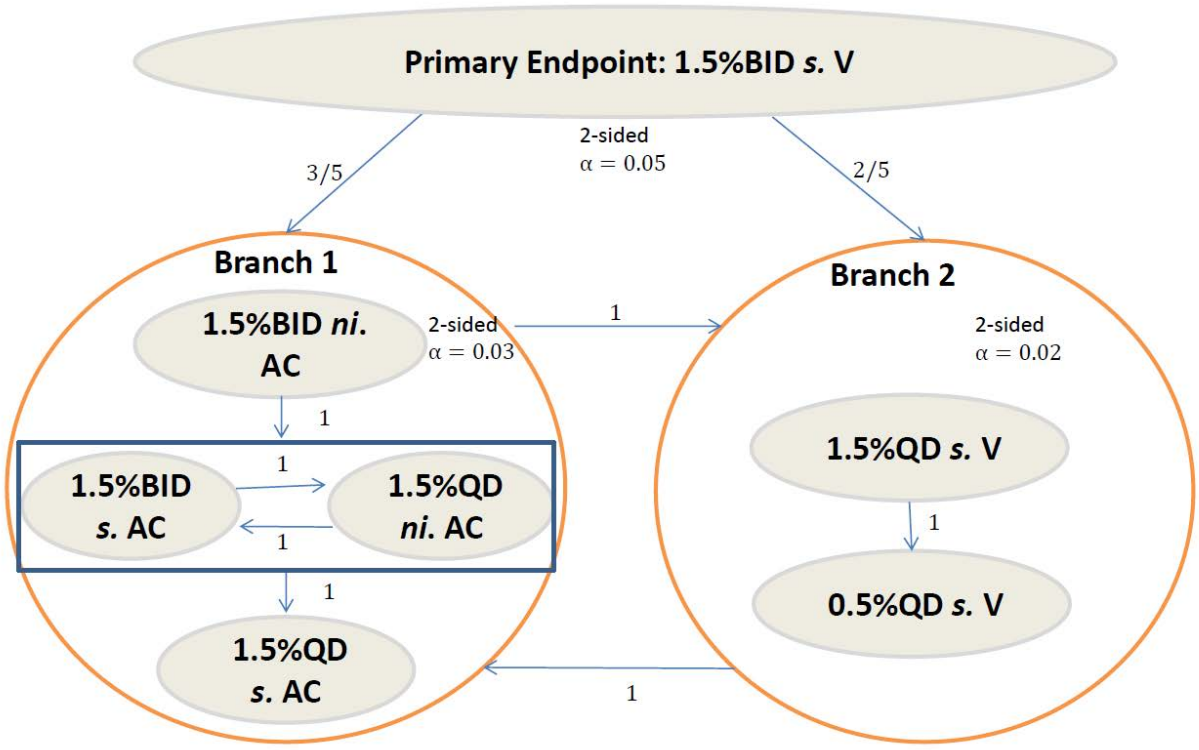
The primary endpoint will test the superiority of INCB018424 1.5% BID compared with vehicle. The key secondary endpoint has 2 branches. Branch 1 will test whether:

- INCB018424 1.5% BID is noninferior to triamcinolone (active control)
- INCB018424 1.5% QD is noninferior to triamcinolone (active control)
- INCB018424 1.5% BID is superior to triamcinolone (active control)
- INCB018424 1.5% QD is superior to triamcinolone (active control)

Branch 2 will test whether:

- INCB018424 1.5% QD is superior to vehicle
- INCB018424 0.5% QD is superior to vehicle

Figure 3: Illustration of the Statistical Treatment Comparisons



AC = active control; s = superiority; ni = noninferiority; V = vehicle.

9.2.1.1. Primary Analysis

The primary alternative hypothesis (superiority of INCB018424 1.5% BID compared with vehicle) will be tested at a 2-sided $\alpha = 0.05$ level. The test on the primary endpoint will be used

as a gatekeeper for 6 statistical tests on secondary endpoints that will be grouped into 2 parallel branches (see Figure 3). The first branch (Branch 1) includes tests of INCB018424 versus triamcinolone. The second branch (Branch 2) includes tests of INCB018424 versus vehicle, as visualized in Figure 3. The initial allocation of the overall significance level to Branch 1 and Branch 2 is three-fifths and two-fifths, respectively. The weights of the level to be passed on if 1 hypothesis is rejected are specified in Figure 3.

9.2.1.2. Secondary Analysis

9.2.1.2.1. Tests in Branch 1

- **Step 1:** The first alternative hypothesis (noninferiority of INCB018424 1.5% BID compared with triamcinolone) will be tested at a 2-sided $\alpha = 0.03$ level if the primary test is significant. If the first alternative hypothesis is established, then hypotheses in Step 2 will be tested at an overall error rate of 0.03.
- **Step 2:** If Step 1 is established, then a superiority test of INCB018424 1.5% BID compared with triamcinolone and noninferiority test of INCB018424 1.5% QD compared with triamcinolone will be carried out using the Bonferroni-Holm procedure at an overall 2-sided $\alpha = 0.03$ level.
- **Step 3:** If both of the null hypotheses in Step 2 are rejected, then a superiority test of INCB018424 1.5% QD compared with triamcinolone will be carried out at a 2-sided $\alpha = 0.03$ level.

If all 4 tests in Branch 1 are significant, then the overall level ($\alpha = 0.03$) of Branch 1 will be reallocated to Branch 2, and the first alternative hypothesis in Branch 2 will be tested with start level of 2-sided 0.05. If 1 or more of the tests in Branch 1 is nonsignificant, there will be no level reallocated from Branch 1 to Branch 2, and the first alternative hypothesis in Branch 2 will be tested with start level of 2-sided 0.02.

9.2.1.2.2. Tests in Branch 2

- Alternative hypotheses (superiority of INCB018424 1.5% QD and 0.5% QD compared with vehicle) will be tested in sequence using the alpha level decided in the previous steps.

If 1 or more of the 4 tests in Branch 1 is nonsignificant, but all tests in Branch 2 are significant, then the alpha level will be reallocated to Branch 1, and Branch 1 will reopen with a start level of 0.05.

9.2.2. Noninferiority Margin

In the historical study (Beck et al 2014), the difference of percentage change from baseline to Day 29 in EASI scores between active control (placebo and glucocorticoids) and placebo was 27.1% with the derived lower limit of 95% confidence interval (CI) 16.4%. Therefore, 27% constitutes the minimum expected benefit of triamcinolone (active control) over vehicle. Given that the result is based on 2 studies with small sample sizes, the margin is chosen to be -10%, which is between a half of the lower 95% CI (-8%) and 50% of the minimum effect (-13.5%).

Noninferiority analysis will be performed between each of the active treatment groups and triamcinolone.

9.2.3. Power Analysis

Given the assumptions specified in Table 5, a simulation following the graphical procedure was performed and showed that a sample size of 50 subjects in each group would yield a power of > 99% to test the superiority of the each of the active treatment group (INCB018424 1.5% BID, INCB018424 1.5% QD, and INCB018424 0.5% QD) to the vehicle group with a 2-sample t test.

Assuming no true difference between the active treatment group and triamcinolone with respect to percentage change from baseline in EASI scores and an SD of 13%, the simulation showed that the sample size of 50 in each group would yield a power of > 99% to declare that the active treatment changes in INCB018424 1.5% BID and INCB018424 1.5% QD are noninferior to triamcinolone (ie, that the lower limit of the 2-sided 95% CI of INCB018424 minus triamcinolone is greater than or equal to the noninferiority margin of -10%). The sample size will also provide at least 95% power to test the superiority of each of the active treatment groups of INCB018424 1.5% BID and INCB018424 1.5% QD to the triamcinolone group.

9.3. Level of Significance

A graphical procedure with a gatekeeping testing strategy for the primary and key secondary analyses will be implemented to control the overall Type I error rate at a 2-sided alpha level of 0.05. The underlying procedure is derived using the methodology developed in Bretz et al (2009). This method will guarantee a strong control of the family-wise error rate.

Simulations results are provided to illustrate Type I error control for the graphical procedure. The Type I error rates, provided in Appendix E, Table E.2, are strongly controlled in all scenarios.

9.4. Statistical Analyses

9.4.1. Efficacy Analyses

9.4.1.1. Efficacy Measures for Primary and Secondary Endpoints

9.4.1.1.1. Eczema Area and Severity Index–50

Eczema Area and Severity Index score is specified in Section 7.6. The categorical variable EASI-50 will be equal to 1 if the percentage improvement from baseline in EASI scores is 50 or greater and 0 if less than 50. This definition is introduced for the purpose of identifying subjects who respond to the treatment (1 - responder, 0 - nonresponder).

9.4.1.1.2. Investigator's Global Assessment Response

Investigator's Global Assessment response is defined as an IGA score of 0 or 1 who have an improvement of ≥ 2 points from baseline.

9.4.1.1.3. Itch Numerical Rating Scale

The Itch NRS score is a single-question assessment tool with a scale of 0 to 10, with 0 being 'no itch' and 10 being 'worst itch imaginable.' The average itch NRS score will be measured overall, for the previous week, and for the previous 24 hours.

[redacted]

9.4.1.2. Primary Efficacy Analyses

Comparisons between INCB018424 1.5% BID and vehicle based on percentage change from baseline in EASI scores at Week 4 will be performed with a fixed-effect ANOVA model using last observations carrying forward in the ITT.

The ANOVA model will include the fixed effects of treatment and randomization stratification factor. If there are no data after the date of randomization, then the endpoint will be considered missing and will not be included in analysis.

Supportive analyses for the primary endpoint include a similar ANOVA approach in the per protocol population.

9.4.1.3. Secondary Efficacy Analyses

Secondary efficacy analyses will be conducted in the ITT population.

The key secondary endpoints will be analyzed using the similar ANOVA as specified in the primary analysis. The graphic approach will be used to control family-wise error rate. Tests for noninferiority between 2 treatment groups will be performed using the least square mean estimate of the percentage change in EASI at 4 weeks. Noninferiority will be established if the lower limit of a 2-sided CI for the difference (INCB018424 minus active control) is higher than or equal to -10%. There will be no adjustment for multiple comparisons for secondary endpoints besides key secondary endpoints.

Mean, change from baseline, and percentage change from baseline of EASI scores at other visits besides Week 4 will be summarized using descriptive statistics. Itch NRS score daily, [redacted] will be summarized and analyzed in a similar fashion.

An E_{max} model will be fit for assessment of the dose response and provide estimates of the maximum and minimum response levels, ED_{50} (the concentration where the response is the midpoint between the maximum and minimum), and the slope parameter.

The categorical endpoints, percentage of subjects with IGA response and subjects achieving an EASI-50 response, will be summarized and may be analyzed by Cochran-Mantel-Haenszel test with stratification factor of randomization.

The Kaplan-Meier product limit method will be used to estimate time–to–EASI-50 response. Treatment comparisons may be performed using the log-rank test stratified by randomization stratification factor, if applicable.

9.4.1.4. Other Efficacy Analyses

Other efficacy variables will be summarized and analyzed using similar methods as described for the primary and secondary endpoints.

9.4.2. Safety Analyses

9.4.2.1. Adverse Events

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

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

9.4.2.2. Clinical Laboratory Tests

Laboratory test values outside the normal range will be assessed for severity based on the normal ranges for the clinical reference laboratory. The incidence of abnormal laboratory values and shift tables relative to baseline will be tabulated.

Laboratory data will be classified into Grades 1 through 4 using CTCAE v4.03. The following summaries will be produced for the laboratory data:

- Number and percentage of subjects with worst postbaseline CTCAE grade (regardless of baseline value). Each subject will be counted only for the worst grade observed postbaseline.
- Shift tables from baseline to the worst postbaseline value using CTCAE grade.
- For laboratory parameters where CTCAE grades are not defined, shift tables to the worst postbaseline value using the low/normal/high classifications based on laboratory reference ranges.

9.4.2.3. Vital Signs

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

9.4.2.4. Twelve-Lead Electrocardiograms

Subjects exhibiting clinically notable ECG abnormalities will be listed.

[redacted]

9.5. Analyses for the 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 may be unblinded.

9.6. Interim Analysis

An interim analysis will be performed when at least half of the randomized or more subjects reach Week 4. Details will be specified in the Statistical Analysis Plan.

10. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

10.1. Investigator Responsibilities

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

The investigator will be responsible for:

- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and subject records at each monitoring visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all subjects.

  - Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.

- Obtaining informed consent and ensuring that the study subjects' questions have been answered and the subjects fully understand study procedures:
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.
  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the subject. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to subject records.
- Obtaining approval from the IRB/IEC before the start of the study and for any changes to the clinical study Protocol, important Protocol deviations, routine updates, and safety information in accordance with institutional requirements and local law.
  - The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by the IRB/IEC.
- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling subjects who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws, but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.
  - All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

10.2. Accountability, Handling, and Disposal of Study Drug

The investigator is responsible for drug accountability of INCB018424 phosphate cream, INCB018424 vehicle cream, and triamcinolone 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 tube counts from each supply dispensed.
- Return of study drug to the investigator or designee by subjects.

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

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

10.3. Data Management

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

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

Protocol deviations will be identified and recorded in the Protocol Deviation form of the eCRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue identified

is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements.

10.4. Data Privacy and Confidentiality of Study Records

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

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

10.5. Financial Disclosure

Before study initiation, all clinical investigators participating in clinical studies subject to FDA Regulation Title 21 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. REFERENCES

Beck LA, Thaçi D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med 2014;371:130-139.

Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. Stat Med 2009;28:586-604.

Clinical Trial Facilitation Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical trials. September 15, 2014. http://www.hma.eu/ctfg.html. Accessed May 26, 2016.

Ellis CN, Drake LA, Prendergast MM, et al. Cost of atopic dermatitis and eczema in the United States. J Am Acad Dermatol 2002;46:361-370.

Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol Suppl (Stockh) 1980;92:44-47.

Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. "The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis." Exp Dermatol 2001;10:11-18.

Hay RJ, Johns NE, Williams HC, et al. The global burden of skin disease in 2010: an analysis of the prevalence and impact of skin conditions. J Invest Dermatol 2014;134:1527-1534.

INCB018424 Phosphate Cream Investigator's Brochure (IB). Wilmington, DE: Incyte Corporation.

Kim BS. Atopic dermatitis. 2015. http://emedicine.medscape.com/article/1049085-overview. Accessed May 26, 2016.

Kim BS, Wang K, Siracusa MC, et al. Basophils promote innate lymphoid cell responses in inflamed skin. J Immunol 2014;193:3717-3725.

Leshem YA, Hajar T, Hanifin JM, Simpson EL. What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study. Br J Dermatol 2015;172:1353-1357.

Levy LL, Urban J, King BA. Treatment of recalcitrant atopic dermatitis with the oral Janus kinase inhibitor tofacitinib citrate. J Am Acad Dermatol 2015;73:395-399.

Poulin Y, Bissonnette R, Papp K, et al. Efficacy and safety of topical Janus kinase inhibitor tofacitinib in the treatment of atopic dermatitis: results of a Phase 2a randomized clinical trial. Presented at: 24th European Academy of Dermatology and Venereology Congress; October 7-11, 2015; Copenhagen, Denmark.

Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other variables: a US population-based study. J Allergy Clin Immunol 2013;132:1132-1138.

Spergel JM. Epidemiology of atopic dermatitis and atopic march in children. Immunol Allergy Clin North Am 2010;30:269-280.

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: CTFG 2014.

APPENDIX B. ECZEMA AREA AND SEVERITY INDEX

The EASI score examines 4 areas of the body and weights them for subjects 8 years of age and older as follows:

Head/Neck (H) = 0.1, Upper limbs (UL) = 0.2, Trunk (T) = 0.3, and Lower limbs (LL) = 0.4.

The percentage of area involved for each of the 4 body regions is weighted as follows: 0 = no eruption, 1 = some to < 10%, 2 = 10% to 29%, 3 = 30% to 49%, 4 = 50% to 69%, 5 = 70% to 89%, and 6 = 90% to 100%.

Each of the 4 body regions is assessed separately for erythema (E), induration/papulation/edema (I), excoriations (Ex), and lichenification (L) for an average degree of severity of each sign in each region with: 0 = none, 1 = mild, 2 = moderate, and 3= severe, with half-step allowed.

Body Region	**EASI Score**
Head/Neck (H)	(E + I + Ex + L) × Area × 0.1
Upper limbs (UL)	(E + I + Ex + L) × Area × 0.2
Trunk (T)	(E + I + Ex + L) × Area × 0.3
Lower limbs (LL)	(E + I + Ex + L) × Area × 0.4
EASI total	Sum of the above 4 body region scores

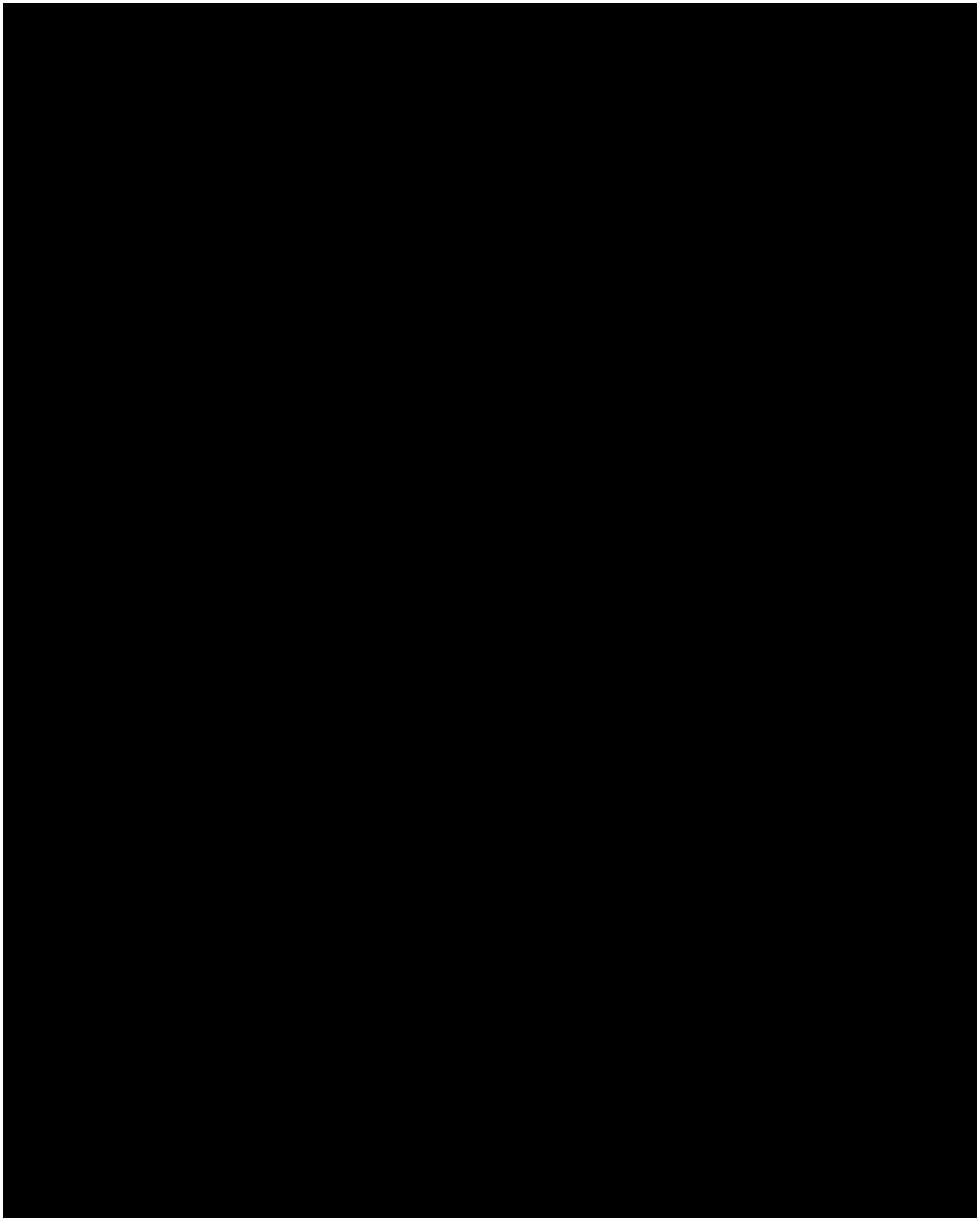
EASI Score Calculation Tool

Body Region	Redness		Thickness		Scratching		Lichenification		Severity Score		Area Score	Multiplier		Region Score
Head/neck		+		+		+		=		×		× 0.1	=	
Trunk		+		+		+		=		×		× 0.3	=	
Upper limbs		+		+		+		=		×		× 0.2	=	
Lower limbs		+		+		+		=		×		× 0.4	=	
Add up the 4 regions to calculate the EASI score													=	

APPENDIX C. POTENT CYP3A4 INHIBITORS AND FLUCONAZOLE

In clinical studies with CYP3A4 inhibitors, elevated levels of INCB018424 of approximately 2-fold have been observed after oral administration. Additionally, simulations using physiologically based 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 if the systemic bioavailability is low may be permitted on a case by case basis. The following is a list of potent CYP3A4 inhibitors and fluconazole. The sponsor should be contacted with any questions regarding concomitant medications that might be considered potent CYP3A4 inhibitors but are not on this list.

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



APPENDIX E. STATISTICAL CONSIDERATIONS

Type I Error Rates

Six scenarios are examined for Type I error rates, corresponding to null hypothesis that there is no different treatment effect between 1 or more active treatment groups with active control or vehicle.

With 50 subjects per group, normal distributions, with standard deviation of 0.13, and mean percentage changes specified in Table E.1 were generated. For each scenario, 10,000 replications were run using SAS® 9.2. Comparisons between each of the active dose to active control or vehicle are performed using 2 sample t-tests. Confidence intervals of the means (INCB018424 - active control or vehicle) were created with corresponding alpha level following the graphical procedure specified in Section 9.2. The lower limits of CIs were compared with the critical values (0 for superiority, and -10% for noninferiority) for treatment comparisons. To provide conservative estimates, the primary comparison (INCB018424 1.5% BID vs vehicle superiority) was excluded from the procedure, that is, only key secondary endpoints were evaluated.

The Type I error rates are provided in Table E.2 under different null hypotheses. The rates are compared with the nominal alpha 2.5%, which showed that the Type I error rates are well-controlled in all scenarios (< 2.5%).

Table E.1: Assumed Percentage Change From Baseline of EASI Score at Week 4 for Type I Error Rates

Scenario	1.5% BID	1.5% QD	0.5% QD	Active Control	Vehicle
S1	40%	40%	40%	50%	40%
S2	50%	40%	40%	50%	40%
S3	60%	40%	40%	50%	40%
S4	40%	40%	40%	50%	30%
S5	50%	40%	40%	50%	30%
S6	60%	40%	40%	50%	30%

Table E.2: 1-Sided Type I Error Rates (%)

Scenarios	S1	S2	S3	S4	S5	S6
Reject at least 1 hypothesis in	T11, T12, T13, T14, or T21 or T22	T12, T13, T14, or T21 or T22	T13, T14, or T21 or T22	T11, T12, T13, or T14	T12, T13, or T14	T13 or T14
Type I error rates	2.44	2.14	2.19	2.34	1.25	1.34

Note: T11: To test whether INCB018424 1.5% BID is noninferior to triamcinolone (active control).
T12: To test whether INCB018424 1.5% BID is superior to triamcinolone (active control).
T13: To test whether INCB018424 1.5% QD is noninferior to triamcinolone (active control).
T14: To test whether INCB018424 1.5% QD is superior to vehicle.
T21: To test whether INCB018424 1.5% QD is superior to vehicle.
T22: To test whether INCB018424 0.5% QD is superior to vehicle.
S1 to S6 are defined in Table E.1.

Signature Manifest

Document Number: eIC-DEV-PROT-0077 **Revision:** 1
Title: INCB 18424-206 Protocol

All dates and times are in Eastern Standard Time.

APPROVAL: 18424-206 Protocol

Approval and Release

Name/Signature	Title	Date	Meaning/Reason
[redacted]	[redacted]	15 Sep 2016, 03:51:00 PM	Approved
[redacted]	[redacted]	15 Sep 2016, 03:52:37 PM	Approved
[redacted]	[redacted]	15 Sep 2016, 10:31:51 PM	Approved
[redacted]	[redacted]	16 Sep 2016, 10:53:44 AM	Approved

Quick Approval

Approve Now

Name/Signature	Title	Date	Meaning/Reason
[redacted]	[redacted]	16 Sep 2016, 11:17:26 AM	Approved