INCB018424 PHOSPHATE CREAM in the Treatment of Cutaneous Lichen Planus

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Study Product: INCB018424 PHOSPHATE CREAM phosphate cream (ruxolitinib)

Protocol Number: (IRBe) 17-005406

IND Number: 139162

Version	Date	Major Changes
1.0	11Sep2017	Initial Protocol
2.0	25Apr2018	Section 9.4 Stopping Rules; Grade 4 reduced to Grade 3
3.0	15Apr2019	Added IND # to cover page 5.1 Inclusion Criteria revised • LP up to 20% of the BSA • Subjects must have a minimum of 4 lesions, ideally 10 lesions of LP 6.6. Drug labeling clarified
4.0	31Oct2019	ECG removed throughout protocol
5.0	08Jan2020	4.1 Up to 60 biopsies will be taken throughout study for analysis 4.3 Table 2 and 7.7 Visit 7 Removed Drug Disbursement at Week 8

		9.1 Supplemental 1: Skin Scoring: Added Lesion Count Methods Updated photos to be taken at every visit from Day 0 through Week 12 visit throughout protocol
6.0	29May2020	Updated CAILS assessment to Modified CAILS throughout protocol

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List of Abbreviations

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
BSA	Body Surface Area
CAILS	Clinical Assessment Scale of Severity for Index Lesion Signs & Symptoms
CFR	Code of Federal Regulations
CRF	Case Report Form
CXCR3	Chemokine Receptor-3
CXCL9	Chemokines Ligands 9
DEGs	Differentially Expressed Genes
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GVHD	Graft Versus Host Disease
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IL-1	Interleukin-1
IND	Investigational New Drug Application
IFNα	Interferon Alpha
IFNγ	Interferon Gamma
IRB	Institutional Review Board
JAK	Janus Kinase
LP	Lichen Planus
LTR	Lichenoid Tissue Reaction
MDC	Myeloid Dendritic Cells
NRS	Numerical Rating Scale
PDC	Plasmacytoid Dendritic Cells
PGA	Physician Global Assessment
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure

Study Summary

Title	**INCB018424 PHOSPHATE CREAM in the Treatment of Cutaneous Lichen Planus**
Running Title	INCB018424 PHOSPHATE CREAM in LP
Protocol Number	17-005406
Phase	Phase II
Methodology	Open-Label, Single Arm
Overall Study Duration	13 to 16 weeks
Subject Participation Duration	12 weeks
Single or Multi-Site	Single Site
Objectives	To evaluate the safety and efficacy of INCB018424 PHOSPHATE CREAM in cutaneous LP as assessed by the change in Physician Global Assessment (PGA), Body Surface Area (BSA), Index Treatment and Control Lesion by Modified Clinical Assessment Scale of Severity for Index Lesion Signs and Symptoms (Modified CAILS) score, Pruritus Numerical Rating Scale (NRS), and Skindex-16. To predict responses through the identification of unique biomarkers of LP at week 0 and utilizing RNA sequencing on responsive and non-responsive tissue at week 4.
Number of Subjects	12
Diagnosis and Main Inclusion Criteria	Non-pregnant adults with cutaneous LP involving less than 20% of the body surface area (BSA)
Study Product, Dose, Route, Regimen	INCB018424 PHOSPHATE CREAM 1.5%, topical application, twice daily on lesions of cutaneous LP.
Duration of Administration	Drug will be administered from Day 0 through Week 8.
Reference therapy	INCB018424 PHOSPHATE CREAM is currently being used to treat subjects with Plaque Psoriasis
Statistical Methodology	The statistical analysis will provide descriptive summary statistics for categorical and continuous outcomes. Categorical variables will be described by their count and proportion of occurrence while continuous, normally distributed variables will be described by their mean and standard deviation; and continuous, non-normally distributed variables will be described by their median and range

2 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

2.1 Background

INCB018424 PHOSPHATE CREAM is a topical JAK1/2 inhibitor with potent activity on the cytokine IFN-γ. IFN-γ is a critical cytokine in the signaling of LP. This study is aimed at evaluating the effects of topical INCB018424 PHOSPHATE CREAM 1.5% twice daily on lesions of cutaneous LP.

Lichenoid tissue reaction (LTR) includes: lichen planus (LP) cutaneous lupus, dermatomyositis (DM), and graft versus host disease (GVHD). The pathogenesis of LP is incompletely understood; however, it is clearly T-cell mediated without a known auto-antigen. Lichen Planus (LP) is an inflammatory skin condition characterized by purple, polygonal, pruritic, papules and plaques. LP can affect any ectodermally derived tissues including: the skin (most commonly), nails, and mucous membranes. LP is thought to affect approximately 1-2% of the general population. Most cutaneous LP resolves within one to two years. Disease duration, in ascending order, is: generalized cutaneous, non-generalized cutaneous, cutaneous and mucosal, mucosal, hypertrophic, and Lichen Planopilaris (hair LP). LP is the prototypical lichen tissue reaction(LTR). Modern theories of LP encompass three major stages: antigen recognition, lymphocyte activation, and keratinocyte apoptosis. A fourth stage, resolution, is a new and emerging topic. The occurrence of triggering factors in a genetically predisposed individual carrying LP-associated genes, results in disease development. During the initiation phase, damage to keratinocytes result in the release of DNA, RNA, and cathelicidin (LL37). These proteins can stimulate plasmacytoid dendritic cells (PDC) via toll like receptors 7, 9 (TLR7,9) which result in the release of interferon alpha (IFNα). IFNα can have both local and distant affects upon myeloid dendritic cells (MDC) as well as keratinocytes. Stimulated MDC interact with CD4+ T-helper cells and with the correct antigen. The antigen remains unknown but may represent a viral derived peptide. Signaling receptors on MDC will stimulate CD4+ T-helper cells via the release of Tumor necrosis factor alpha (TNFα), Interleukin-1 (IL-1), and -12. In addition, cluster of differentiation- (CD40) and CD40 ligand (CD40L) will result in the co-stimulation of the T-helper/MDC interaction. Stimulated CD4+ T-helper cells then release of interferon gamma (IFNγ) and IL-2. These cytokines stimulate CD8+ T-cytotoxic cells. The stimulated CD8+ cells expressing Chemokine receptor-3 (CXCR3) will migrate to the dermal-epidermal junction following the release of chemokines ligands 9(CXCL9), -10,-11. These chemokines are released by stressed and stimulated keratinocytes. The stimulated CD8+ cells will interact with the stressed keratinocytes and can induce apoptosis in with the proper and signaling receptors. This antigen also remains unknown but may be a self-antigen released by local stress. The major kill signals are TNFα, granzyme, and perforin. Fas and Fas ligand (FasL) are expressed on both keratinocytes and lymphocytes. Local CXCR3+ DC and T-regulatory cells may also modulate the local lichenoid response.

Based upon critical role of CD8+ T-cytotoxic cells and IFNα and IFNγ signaling in LP, inhibition with topical Janus Kinase (JAK) 1, 2 inhibitors have significant therapeutic potential. The current

topical therapeutic options for LP are limited to topical corticosteroids, calcineurin inhibitors, and retinoids. Topical therapies are effective with limited disease but refractory disease is frequently encountered. Specific variants of LP, such as hypertrophic LP and localized cutaneous disease, are often refractory to all topical therapies and require systemic or skin-directed treatment with oral acitretin or methotrexate or light therapy. Therefore, additional topical therapies would be highly desirable in hypertrophic and refractory localized cutaneous LP. As proof of principle, systemic JAK1, 2 inhibition with ruxolitonib was highly effective in steroid refractory graft versus host disease (GVHD). (1) Additionally, there was a recent case report of an exceptional responder to JAK1, 2 inhibition with ruxolitinib in refractory dermatomyositis (DM). (2) As stated above, DM, GVHD, and LP share a similar histological pattern as well as signaling mechanism and, therefore, we would expect LP to respond similarly with systemic as well as topical treatment. To test this concept, we would propose a single-center, exploratory, open-label, single-arm design study using topical JAK1, 2 inhibitor on selected lesions of LP.

2.2 Investigational Agent

INCB018424 PHOSPHATE (ruxolitinib) is an inhibitor of the JAK family of protein tyrosine kinases. Mitogenic and inflammatory cytokines are strongly implicated in the pathogenesis of psoriasis, alopecia areata, atopic dermatitis, and lichenoid tissue reactions of the skin including LP. INCB018424 PHOSPHATE CREAM also potently inhibited the phosphorylation of STAT proteins and the production of pro-inflammatory factors induced by cytokines such as IL-23 and IFNγ. (Investigator's Brochure) IFNγ is a key cytokine in the pathogenesis of LP.

INCB018424 PHOSPHATE CREAM 1.5%, topical application, twice daily on lesions of cutaneous LP.

2.3 Preclinical Data

The absorption, pharmacokinetics (PK), distribution, and metabolism of INCB018424 were characterized in CD-1 mice, rats, cynomolgus monkeys, beagle dogs, and Gottingen minipigs, and the metabolism of INCB018424 was characterized in vitro in rat, dog, and human and in vivo in CD-1 mouse, rat, dog, minipig, and human. Additional studies include the mass balance excretion of 14C-INCB018424 in rats, dogs, and humans after oral dosing, the tissue distribution in rats after an oral dose, and the skin distribution in Gottingen minipig after daily topical administration.

The relative bioavailability of INCB018424 PHOSPHATE CREAM was markedly (~ 90%) lower than that following oral administration. Following intravenous (IV) administration of INCB018424, the total systemic clearance was species-dependent, ranging from 26% (dog) to 450% (minipig) of hepatic blood flow. The primary clearance pathway is via metabolism based on the identification of multiple metabolites coupled with negligible renal clearance of parent drug in all species studied. In vitro metabolism studies strongly suggest that cytochrome P450 (CYP) 3A4 is the predominant CYP isozyme responsible for the metabolism of INCB018424.

The major metabolites in rat, dog, and the minipig were the hydroxylated products and the corresponding ketones. All INCB018424 human in vitro metabolites were also present in rat, dog, and minipig. Several in vitro and/or in vivo metabolites of INCB018424 found in rat, dog, and human retain JAK-related pharmacological activity.

In CD-1 and hairless (CrL:SKH1-hr) mice after topical dosing for up to 3 months, there were minimal differences in the plasma toxicokinetics of INCB018424 PHOSPHATE CREAM. The distribution and elimination was rapid, while the AUC values for INCB018424 were not consistently different between steady state and Day 1. Higher application rates resulted in higher exposures, which further increased when administered twice daily (BID) compared to once daily (QD). The in vitro transdermal flux of INCB018424 in a solubilized cream formulation across mouse skin was about 20-fold higher than with human cadaver skin.

In Gottingen minipigs following a single topical application using either a 1.5% w/w solubilized cream or a 1.0% w/w dispersed cream, INCB018424 exhibited an apparent zero-order transdermal absorption with an average plasma concentration over 24 hours of about 1 nM. In toxicology studies in minipigs up to 9 months using the solubilized cream formulation, plasma concentrations of INCB018424 were significantly higher at steady state compared to Day 1. There were minimal sex differences in plasma AUC values, which were higher when administered BID compared to QD.

In rats, elimination of drug-derived radioactivity after a single oral and IV dose was rapid, with excretion in urine, bile, and feces accounting for approximately 50%, 37%, and 12% of the dose, respectively. Elimination was rapid in male and female dogs after an oral dose, with excretion in urine and feces accounting for 34% to 36% and 55% to 58% of the dose, respectively. These results are similar to humans, which after a single oral dose of 14C-INCB018424 PHOSPHATE CREAM, recovery of administered radioactivity was 96% (74% in urine and 22% in feces).

The apparent steady-state volume of distribution (Vss) of INCB018424 ranged from 0.81 L/kg (monkey) to 6.4 L/kg (minipig), and the terminal elimination half-life ranged from 0.4 hour (rat) to 2.5 hours (dog). In Sprague Dawley rats, after oral dosing, the highest concentrations were observed in the tissues and contents of the gastrointestinal tract, urinary bladder, renal cortex, 12 renal medulla, liver, aorta, and adrenal gland. In Long Evans rats, the highest concentrations of drug-derived radioactivity were tissues and contents of the gastrointestinal tract, urine, bile, uveal tract, liver, renal medulla, renal cortex, skin (pigmented), and kidney. Elimination in Sprague Dawley and Long Evans rats was rapid and complete in most tissues. In a male Gottingen minipig after 4 consecutive daily topical doses of 1% 14C-INCB018424 cream, radiolabeled material penetrated from the site of application into the epidermis, while penetration into the underlying dermis was substantially lower. The serum and plasma protein binding of INCB018424 was species-dependent, with fraction unbound ranging from 2.7% in CD-1 mice to 33% in the minipig (human in vitro unbound fraction in plasma was 3.3%).

The toxicologic and toxicokinetic profiles of INCB018424 were characterized in single and repeat oral dose studies of up to 4 weeks in mice, 6 months in duration in rats, and 12 months in duration in dogs, and in single and repeat topical dose studies of up to 3 months in mice and up to 9 months in the Gottingen minipig. INCB018424 was evaluated in acute dermal and ocular

irritation studies in rabbits, an acute ocular irritation study in dogs, 10-day ocular toxicity studies in rabbits and dogs, the mouse local lymph node assay, and in phototoxicity and photoallergy studies in hairless albino guinea pigs. Genetic toxicology, safety pharmacology, and reproductive toxicology assessments have also been conducted, and the carcinogenic potential of INCB018424 was evaluated in a 6-month Tg.rasH2 transgenic mouse model and in oral and topical 2-year carcinogenicity studies in rats and mice, respectively.

INCB018424 PHOSPHATE CREAM applied at concentrations ≤ 1.5% BID, using a 10 mg/cm2 application rate to 10% body surface area (BSA) was well tolerated in assessments of up to 9 months in the Gottingen minipig. Decreases in lymphocytes were observed in both male and female animals administered INCB018424 but were considered nonadverse in the absence of any other findings suggestive of systemic toxicity. INCB018424-associated microscopic skin lesions were generally of minimal to mild severity and lacked a clear dose-response relationship. The no-observed-adverse-effect level (NOAEL) was 1.5% BID (Day 293 mean unbound AUC 0.064 μM*h). INCB018424 PHOSPHATE CREAM did not act as a contact sensitizer nor did it produce significant dermal or ocular irritation, acute phototoxicity, or photoallergic potential. There was no evidence of systemic toxicity following repeated ocular administration to rabbits or dogs.

Effects noted in multiple-dose oral toxicity studies were primarily those associated with the mechanism of action of INCB018424. Decreases in red blood cells, reticulocytes, eosinophils, and lymphocytes have been observed along with lymphoid depletion in bone marrow and lymphoid organs. In addition, in dogs, demodectic mange, bacterial pneumonia, and viral-induced papillomas, expected consequences of the pharmacology of JAK inhibition, were noted. INCB018424 doses ≥ 50 mg/kg given to rats as a single oral dose in a central nervous system evaluation were associated with decreases in body temperature and transient decreases in locomotor activity. Administration of single oral doses of 150 mg/kg INCB018424 was associated with decreases in respiratory frequency, increases in tidal volume, and, for females only, an adverse decrease in minute volume. The IC50 for inhibition of the human-ether-à-go-go related gene (hERG) channel was determined to be 131.6 μM. In a cardiovascular evaluation of INCB018424 in radiotelemetry-implanted dogs, electrocardiogram (ECG) parameters were unaffected at all doses. Administration of 30 mg/kg INCB018424 resulted in an adverse lowering of systolic, diastolic, mean arterial, and pulse pressures with a corresponding increase in heart rate. There were no effects on ventricular repolarization at any dose in the study.

In embryo-fetal assessments in rat and rabbit, maternal toxicity and minimal embryo-fetal toxicity were noted at the highest doses evaluated. INCB018424 was not teratogenic in either species. The NOAEL dose for the rat and rabbit study was 30 mg/kg per day. In an evaluation of fertility and early embryonic development, no effects were noted on reproductive performance or fertility in male or female rats. Increases in postimplantation loss were noted at the higher doses. In a prenatal and postnatal development and maternal function study in rats, there were no adverse findings for fertility indices or for maternal and embryo-fetal survival, growth, and developmental parameters. INCB018424 passed into the milk of lactating rats with an exposure that was 13-fold higher than maternal plasma exposure.

INCB018424 was not mutagenic or clastogenic, nor did it demonstrate potential for carcinogenicity in a 6-month study in Tg.rasH2 mice or in 2-year studies in mice or rats.

2.4 Clinical Data to Date

INCB018424 PHOSPHATE CREAM has been evaluated in over 200 subjects with plaque psoriasis in 3 clinical studies with dosing of 1 to 3 months' duration.

Study INCB 18424-201 was a double-blind, vehicle-controlled, rising-dose, safety, tolerability, PK, and preliminary efficacy study of INCB01824 1% cream applied QD and 1.5% cream applied BID. All doses were safe and well tolerated. Preliminary efficacy was consistently shown for the 1.0% QD and 1.5% BID cohorts compared with vehicle, with a trend toward a dose response. The 1.5% cream BID showed similar responses compared with Dovonex® (calcipotriene) 0.005% cream and Diprolene® AF (betamethasone dipropionate) 0.05% cream. Systemic bioavailability of INCB018424 was independent of formulation strength. All adverse events (AEs) were mild to moderate in intensity and most judged unrelated to study medication, with no associated serious AEs (SAEs) or withdrawals. Laboratory and ECG evaluations did not suggest any safety issues, specifically no instances of neutropenia, thrombocytopenia, or leukopenia.

INCB 18424-202 was an open-label, multicenter, sequential-cohort, dose-escalation, safety, tolerability, PK, pharmacodynamic (PD), and preliminary efficacy study of INCB018424 PHOSPHATE CREAM 1.0% or 1.5% applied to 2% to 20% BSA QD or BID for 4 weeks. Application area increased sequentially, and alternative dosing paradigms were explored at the highest application area. The efficacy analyses collectively demonstrated efficacy of all 5 regimens of INCB018424 PHOSPHATE CREAM in psoriasis. The incidence of all reported AEs, the clinical laboratory results, vital signs, and ECG findings showed no confirmed safety signals or trends. Mean topical bioavailability ranged from 3.4% to 5.2% with no significant inhibition of cohort mean PD. Overall, INCB018424 PHOSPHATE CREAM (1.0% or 1.5%) was demonstrated to be safe and well tolerated when applied QD or BID for 28 days to plaque psoriasis affecting 2% to 20% of the BSA.

INCB 18424-203 was a double-blind, randomized, multicenter, parallel group, vehicle-controlled dose-ranging study with application of INCB018424 PHOSPHATE CREAM or vehicle in subjects with stable plaque psoriasis The study was designed to evaluate safety and efficacy of INCB018424 PHOSPHATE CREAM
0.5%, 1.0%, or 1.5% relative to vehicle cream when applied QD for 12 weeks in equal size groups.

Overall, 199 subjects were enrolled. A total of 161 (80.9%) completed the Day 84 visit. Within each active treatment group, the mean scores for the individual and total psoriasis lesion assessments, the Psoriasis Area and Severity Index (PASI), and the Physician's Global Assessment (PGA), as well as the mean treatable percent BSA decreased from baseline to each subsequent assessment, which indicated an overall lessening of disease severity. Based on a review of the extent of exposure, the incidence of all reported AEs, the clinical laboratory results, vital signs, and ECG findings, no safety signals or trends were observed. Overall, INCB018424

PHOSPHATE CREAM (0.5%, 1.0%, or 1.5%) was demonstrated to be safe and well tolerated when applied QD for 12 weeks to plaque psoriasis affecting 2% to 20% of the BSA.

Study INCB 18424-204 is a 2-part study of subjects with alopecia areata with Part A being open-label and Part B being double-blind, randomized, and placebo-controlled; subjects in both parts who meet prespecified criteria are eligible for an additional 24 weeks of open-label treatment. Preliminary unaudited data for this study are presented through 28 JUN 2016. Twelve subjects were enrolled in Part A, the open-label portion of the study. Of these 12 subjects, 5 subjects (41.7%) have completed the study through Week 24, and no subjects have discontinued study treatment. Forty-four subjects were randomized in Part B, the double-blind portion of the study. Of these 44 subjects, 3 subjects (6.8%) discontinued from the study, 1 subject because of an AE (pruritus judged not related to study drug), 1 subject because of subject decision, and 1 subject because of abnormal laboratory values at screening. In Part A, 8 subjects (66.7%) had a treatment-emergent adverse event (TEAE). One subject had Grade 3 SAEs of noncardiac chest pain, pulmonary mass, and sepsis judged as not related to study drug by the investigator that led to interruption of study drug; these events resolved, and the subject resumed study drug. All of the TEAEs reported in Part A occurred in 1 subject each. In Part B, 7 subjects (16.7%) had TEAEs. One subject had an SAE of nausea and vomiting (judged not related by the investigator); this event resolved with continuation of study drug. The most frequently reported TEAE in Part B was skin exfoliation, which was reported in 3 subjects (7.1%); these events were judged as not related by the investigator.

INCB018424 has also been administered orally as single or multiple doses to healthy volunteers and subjects with inflammatory, hematologic, and oncologic disease. Oral administration has been generally safe and well tolerated. Literature reports also indicate that oral INCB018424 may restore hair growth in patients with alopecia areata.

INCB018424 PHOSPHATE CREAM appears to pose a low risk of cutaneous toxicity. INCB018424 PHOSPHATE CREAM applied at concentrations ≤ 1.5% (10 mg/cm2 application rate to 10% BSA corresponding to 434-1099 cm2) was well tolerated in a 9-month assessment in the Gottingen minipig. INCB018424 PHOSPHATE CREAM did not act as a contact sensitizer nor did it produce significant dermal irritation or demonstrate phototoxicity or photoallergenic potential. This lack of adverse cutaneous effects has been supported by clinical trials to date where cutaneous AEs have been infrequent and of similar frequency and severity as with vehicle control treatment. INCB018424 PHOSPHATE CREAM tested positive in a photoclastogenicity assay; hence there may be a risk of skin reaction to the combined exposure of INCB018424 PHOSPHATE CREAM and sunlight. 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.

The primary clinical risks noted with orally administered INCB018424 treatment are the potential sequelae of decreased hematopoietic proliferation secondary to the inhibition of growth factor pathways by JAK2 antagonism. Systemic exposure with topical INCB018424 PHOSPHATE CREAM is several fold below that which is associated with hematologic changes that may be seen following oral dosing. Dose-dependent, reversible thrombocytopenia has been

observed in subjects with myelofibrosis (MF), as well as anemia and less frequently neutropenia. An increased rate of infection is an additional potential risk of immunomodulation. A few subjects have had an apparent worsening of their premorbid disease symptoms following rapid cessation of INCB018424 therapy. A gradual tapering and use of steroids in fragile patients may be considered when stopping INCB018424 therapy. Leukemic transformation has been observed, but was considered to be consistent with the natural history of the underlying disease and unrelated to drug. In healthy volunteers and rheumatoid arthritis (RA) patients with greater bone marrow reserve, the effects on hematopoietic proliferation appear to be less pronounced. Overall, the safety profile of ruxolitinib in the polycythemia vera (PV) population treated was generally consistent with what was observed in the MF population. Ruxolitinib was generally well tolerated in subjects with PV, and only a small proportion of subjects discontinued ruxolitinib due to AEs (3.6%). Most of the AEs have been managed by dose adjustments. Hematologic toxicities were less frequent and less severe in subjects with PV as compared to those observed in subjects with MF.

2.5 Dose Rationale

Topical Dosing:
In addition to the safety pharmacology and toxicology studies that were completed to support development of INCB018424 PHOSPHATE CREAM. The relative bioavailability of INCB018424 PHOSPHATE CREAM was markedly (~ 90%) lower than that following oral administration. In vitro metabolism studies strongly suggest that cytochrome P450 (CYP) 3A4 is the predominant CYP isozyme responsible for the metabolism of INCB018424 PHOSPHATE CREAM.

INCB018424 PHOSPHATE CREAM has been evaluated in over 200 subjects with plaque psoriasis in 3 clinical studies with dosing of 1 to 3 months' duration. Study INCB 18424-201 was a double-blind, vehicle-controlled, rising-dose, safety, tolerability, PK, and preliminary efficacy study of INCB01824 1% cream applied QD and 1.5% cream applied BID. All adverse events (AEs) were mild to moderate in intensity and most judged unrelated to study medication, with no associated serious AEs (SAEs) or withdrawals. Laboratory and ECG evaluations did not suggest any safety issues, specifically no instances of neutropenia, thrombocytopenia, or leukopenia.

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INCB 18424-203 was a double-blind, randomized, multicenter, parallel group, vehicle-controlled dose-ranging study with application of INCB018424 PHOSPHATE CREAM or vehicle in subjects with stable plaque psoriasis. Overall, INCB018424 PHOSPHATE CREAM (0.5%, 1.0%, or 1.5%) was demonstrated to be safe and well tolerated when applied QD for 12 weeks to plaque psoriasis affecting up to to 20% of the BSA." **(Investigator's Brochure)**

2.6 Risks and Benefits

Benefits:

Others with LP may benefit in the future from what we learn in this research study. It is possible their symptoms could also improve while being treated with this study drug

Risks:

The following adverse events were reported as very common Side effects associated with the use of INCB018424 PHOSPHATE CREAM:

- Occurring in greater than or equal to 10% of subjects), common (occurring in 1-10% of subjects), and rare (occurring in 0.1% of subjects) side effects occurring in 203 subjects with psoriasis treated with INCB018424 PHOSPHATE CREAM up to 1.5% twice daily strength (the highest strength to be used in this study) in 3 previous studies. Additionally, 54 subjects with alopecia areata (immune-related condition of hair loss) are participating in an ongoing study.

Very Common (affecting more than 10 in every 100 patients)
No adverse event was seen in more than 10% of the psoriasis subjects treated with INCB018424 PHOSPHATE CREAM up to 1.5% twice daily

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Common (affecting less than 10 in every 100 patients)	
Upper respiratory tract infection/nasopharyngitis (common cold)	Abdominal pain (stomach pain)
Application site irritation (irritation on skin where study treatment is applied)	Muscle strain
Headache	Throat Pain
Change in ECG tracing	Psoriasis (skin disorder under treatment)
Pruritus (itching)	Blood sugar increased
Sinusitis (sinus infection)	Cholelithiasis (stone in gall bladder)
Back Pain	Cough
Diarrhea	Cystitis (irritation of bladder)
Dry Skin	Skin redness
Liver enzyme increased	Bulging disk in back
Gastroenteritis (vomiting/diarrhea caused by virus)	Blood cell count decreased
	Pneumonia (lung infection)
	Fever
	Skin peeling

Common (affecting less than 10 in every 100 patients)	
Influenza (flu)	Toothache

Rare but Serious
In seven out of 203 patients treated, serious adverse events were observed but were considered unrelated to INCB018424 PHOSPHATE CREAM use. Due to the number of patients studied to date, rare serious adverse events cannot be predicted with any certainty.

Photosensitivity:
There may be a risk of skin reaction to the combined exposure of INCB018424 PHOSPHATE CREAM and sunlight.

Hematologic abnormalities:
INCB018424 taken systemically can inhibit the growth of blood cells. Low blood cells can make subjects more susceptible to infections by bacteria, virus, and fungi. The risk is low with systemic therapy and was not noted with topical therapy but subjects will be monitored for any signs of inhibition of their blood counts.

Infection risk:
There is a theoretical increase in risk of infection with topical use of INCB018424 PHOSPHATE CREAM. This will be monitored for.

INCB018424 may increase risk of infections and reactivation of latent infections such as Tuberculosis or Valley Fever. Serious bacterial, fungal and viral infections were observed in patients receiving INCB018424. Please seek medical advice if signs or symptoms suggestive of infection occur.

Allergy:

It is possible that some people could have an allergic reaction to INCB018424 PHOSPHATE CREAM.

Cancer Risk:
INCB018424 PHOSPHATE CREAM may have the potential to affect subject's immune system; they may be at increased risk for infections and possibly cancer. Live vaccines should not be given concurrently with INCB018424 PHOSPHATE CREAM.

Pregnancy Risk:

The effect of the study drug on a fetus (developing baby still in the womb), or on a breastfeeding infant, is unknown and may be harmful. Because of these risks, women cannot take part in this study if they are pregnant or breastfeeding.

Skin biopsy:
A skin biopsy is generally a safe procedure, but some potential risks may include local pain, mild local bruising, bleeding, scarring, and an infection at the site where the skin biopsy was performed. If a topical antibiotic is used afterwards, then there is a small risk of an allergic reaction.

Chest X-ray:
Subjects will be exposed to radiation from the chest x-ray. The amount of radiation has a low risk of harmful effects.

Blood draw:
The risks of drawing blood include pain, bruising, lightheadedness, and/or fainting, or rarely, infection at the site of the needle stick.

Other:
As with all research, there is a chance that confidentiality could be compromised; however, we take precautions to minimize this risk.

3 Study Objectives

Primary Objective:
To determine the efficacy of INCB018424 PHOSPHATE CREAM as measured by the change in Modified CAILS score of the index treatment and control lesion (weeks 0 and 4) and changes in lesion count (week 0 and 4)

Secondary Objective:
To determine the efficacy of INCB018424 PHOSPHATE CREAM and the duration of response after discontinuation as measured by the change in Pruritus NRS, (week 0 to week 4, week 0 to week 8, weeks 4 to 8, weeks 8 to 12), Change in Skindex-16 (week 0 to week 4, weeks 4 to 8, weeks 8 to 12), Change in Physician Global Assessment (PGA) (week 0 to week 4, week 0 to week 8, weeks 4 to 8, weeks 8 to 12), Change in BSA (week 0 to week 4, week 0 to week 8, weeks 4 to 8, weeks 8 to 12), Change in Modified CAILS (week 0 to week 8, weeks 4 to 8, weeks 8 to 12).

Exploratory Objectives:
To predict responses and examine the pharmacodynamics of treatment through the identification of unique biomarkers and transcriptomic changes of LP at week 0 and utilizing RNA sequencing on responsive and non-responsive tissue at week 4 To correlate these biomarkers with measures of global response: Modified CAILS, PGA, BSA, and lesion count.

4 Study Design

4.1 *General Description*

This is a single center, exploratory, open-label, single-arm design study of 12 patients. Treatment naïve and treatment refractory patients with LP will be treated with INCB018424 PHOSPHATE CREAM. Patients who are non-responders, to physician choice standard of care, will undergo a washout period and will be enrolled in the study.

Multiple safety studies have been conducted with INCB018424 PHOSPHATE CREAM (see Safety) and a dose of 1.5% cream BID on up to 20% BSA is deemed safe. (Investigator's Brochure) The Within each cohort, the maximum reduction from baseline in the total psoriasis lesion assessment scores for the treated lesions was observed at the end of treatment (Day 28). (Investigator's Brochure) Therefore, we propose a single center, exploratory, open-label, single-arm design study of 12 patients. Treatment naïve and treatment refractory patients with LP will be treated with INCB018424 PHOSPHATE CREAM.

Individuals with LP involving less than 20% of the BSA will be eligible. Individuals must have 4 lesions at baseline, however, a minimum of 10 lesions is ideal, which are at least 5mm in diameter. 10 lesions are ideal as 2 lesions will be index lesions and 8 or more lesions will be selected from as responsive or non-responsive at 4 weeks. All lesions except for one index lesion will be treated and all lesions will be annotated, photographed, and scored. The rationale for a minimum of 8 lesions is based upon the assumption of a 50% response rate at 2 weeks. With 8 lesions, there would be a less than 1% chance that all 8 lesions would respond. Ideally, the 2 index lesions will be 10mm in diameter but this is not a requirement. Prior treatment will be allowed; however, a washout period of 2 weeks for topical and 4 weeks for systemic agents is required. At the washout period, individuals will undergo evaluation with a PGA, BSA calculation, and have the 2 largest, representative lesions selected for evaluation using a modified CAILS score lesion A- treatment index lesion and B-index control lesion. The determination of which lesion receives treatment and which is a control will be determined randomly. The additional lesions will be photographed, measured, scored, and recorded with Modified CAILS scores as well. The later calculations will be used for the determination of responsive and non-responsive lesions. Additional Pruritus measures using the NRS and Skindex-16 will be collected at that time.

Individuals will then initiate treatment on all lesions of LP BID and will be evaluated weekly and assessed by PGA, BSA, lesion count; Modified CAILS, Pruritus NRS, and Skindex-16 between weeks 0-4 (see Appendix). Week 4 will be the primary endpoint; however therapy will be continued for an additional 4 weeks. Therapy will be stopped and the individuals will be evaluated at week 8 and assessed by PGA, BSA, lesion count, Modifed CAILS, Pruritus NRS, and Skindex-16. Laboratory and safety monitoring will occur at weeks 1, 2, 3, 4, and 8, and 12. 3D Photographs will be taken at weeks 0, 1, 2, 3, 4, 8, and 12. Individual lesions will be circled at that time and the exact volume of each lesion will be measured. Up close photos will be taken of the disease and normal tissues attained at weeks 0 & 4.

Tissue will be collected for RNA sequencing at week 0 and 4. Blood collection will include the isolation at week 0, 2, and week 4, 5mL vials of blood which will be separated and the serum and cell pellet will be stored for future analysis. Five skin biopsies will be taken during the study. At week 0, up to two 3mm tissue biopsies will be taken from lesional skin and one biopsy will be taken from normal appearing skin. The initial biopsy of lesional tissue and control will be

annotated. At week 4, up to two 3mm biopsies will be taken from lesional responsive tissue and lesional refractory tissue. Responsive and non-responsive lesions will be determined by the change in Modified CAILS between week 0 and 4. Responsive will require a 50% reduction in Modified CAILS and non-responsive can have progression, no change, or up to a 50% reduction in Modified CAILS. The lesions will be chosen using full body photographs taken at week 0. Up to 60 samples will be snap frozen and stored in the tissue biobank. Once completed, RNA sequencing will be performed on the 60 tissue samples and analysis will be performed. Paired analysis of treatment responsive and refractory lesions will be made as well as treated and untreated lesions.

Nucleic Acid Extractions: RNA will be extracted from a total of 50 um of fresh tissue using the Qiagen FFPE RNeasy Micro extraction Kit according to manufacturer's recommendation.

RNA Transcriptome Sequencing: RNA transcriptome sequencing will be carried out using commercially available techniques. Briefly, RNA Libraries will be created using up to 100ng of RNA as starting material using the Agilent RNA Access Library kit according to manufacturer's recommendation. Libraries will be QCed for quality and quantity using the Agilent BioAnalyzer High Sensitivity Chip. Pair-End sequencing will then be carried out on the Illumina HiSeq 4000 using 101bp insert fragments.

Primary and Secondary Measures:

All efficacy assessments will be performed prior to the administration of study treatment at each visit. The recommended order and the overall outline of measurements for the efficacy assessments are described below.

Efficacy measures: PGA, BSA, Modified CAILS, Pruritus NRS, Skindex-16
To determine the efficacy of INCB018424 PHOSPHATE CREAM as measured by the change in Modified CAILS score of the index treatment and control lesion (weeks 0 and 4) and changes in lesion count (week 0 and 4)

Secondary Outcome Measures: To determine the efficacy of INCB018424 PHOSPHATE CREAM and the duration of response after discontinuation as measured by the change in Pruritus NRS, (week 0 to week 4, week 0 to week 8, weeks 4 to 8, weeks 8 to 12), Change in Skindex-16 (week 0 to week 4, weeks 4 to 8, weeks 8 to 12), Change in Physician Global Assessment (PGA) (week 0 to week 4, week 0 to week 8, weeks 4 to 8, weeks 8 to 12), Change in BSA (week 0 to week 4, week 0 to week 8, weeks 4 to 8, weeks 8 to 12), Change in Modified CAILS (week 0 to week 8, weeks 4 to 8, weeks 8 to 12).

Exploratory Outcome Measures: To predict responses and examine the pharmacodynamics of treatment through the identification of unique biomarkers and trasnscriptomic changes of LP at week 0 and utilizing RNA sequencing on responsive and non-responsive tissue at week 4 to correlate these biomarkers with measures of global response: Modified CAILS, PGA, BSA, and lesion count.

4.2 Number of Subjects

12 subjects will be enrolled in this study.

4.3 Duration of Participation

The study consists of 3 epochs: screening/washout period (of at least 1 week and up to 4 weeks), treatment epoch (of 8 weeks from screen/washout), and follow up epoch (of 4 weeks). The screening and washout period will allow for treatment naïve/ new diagnosis LP to undergo evaluation and diagnosis and for treatment refractory to undergo a washout. The total duration of the study will be 13-16 weeks.

Tables:

- **Table-1: Prohibited treatment**

Prohibited treatments[†, ‡]	**Washout period (before Randomization Visit)**
Any concomitant oral or topical JAK inhibitor	Prohibited
Any biologic drug	Stable dose for 3 months
Immunomodulation treatments for LP[§] [e.g., methotrexate, cyclosporine A, corticosteroids (oral, i.v., intramuscular, s.c., intra-articular, transdermal), mycophenolate mofetil, azathioprine]	4 weeks
Topical treatment that is likely to impact signs and symptoms of LP (e.g., pimecrolimus, tacrolimus)	2 weeks
Non-immunosuppressive agents (tetracycline antibiotics & niacinamide)	2 weeks
Prohibited regimen of Topical Corticosteroids (TCS)	
TCS on any location on body (including face, scalp and/or genitoanal area)	2 weeks

[†] If the prohibited treatment is being used during the study for any indication, the subject must discontinue use of the prohibited treatment if he/she wishes to continue in the study.
[‡] In case of undue safety risk for the subject, the subject should discontinue study treatment at the discretion of the investigator/qualified site staff. If the subject received a live virus vaccination during the study, the subject must discontinue study treatment.
[§]Inhalative CS with only a topical effect (e.g., to treat asthma) are not considered "systemic immunomodulation treatments" and are therefore acceptable as co-medication. Immunosuppressive medication for conditions other than LP will be allowed.

Table-2: Screening and Visits (+/- 2 day window)

	Screening	Day 0	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12

INCB18424		X	X	X	X	X		
Physical Exam	X	X	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X	X
Chest X-ray	X							
Assessments: PGA, BSA, lesional number, Modified CAILS, Skindex-16, Pruritus NRS		X	X	X	X	X	X	X
Photographer		X	X	X	X	X	X	X
Skin Biopsy (tissue/serum bank)		X				X		
Urine Pregnancy Test	X							
Venipuncture	X	X	X	X	X	X	X	X
Biomarker/RNAseq blood (tissue/serum bank)		X		X		X		
CMP	X		X	X	X	X	X	X
CBC	X		X	X	X	X	X	X
Quantiferon Gold	X							
Hepatitis B	X							
Hepatitis C	X							
HIV	X							
Coccidioidomycosis	X							

4.4 Primary Study Endpoints

Change in Modified CAILS of index treatment lesion and index control lesion (week 0 and 4) and change in lesion count (week 0 and week 4).

4.5 Secondary Study Endpoints

Change in Pruritus NRS, (week 0 to week 4, week 0 to week 8, weeks 4 to 8, weeks 8 to 12), Change in Skindex-16 (week 0 to week 4, weeks 4 to 8, weeks 8 to 12), Change in Physician Global Assessment (PGA) (week 0 to week 4, week 0 to week 8, weeks 4 to 8, weeks 8 to 12), Change in BSA (week 0 to week 4, week 0 to week 8, weeks 4 to 8, weeks 8 to 12), Change in Modified CAILS (week 0 to week 8, weeks 4 to 8, weeks 8 to 12).

4.6 Primary Safety Endpoints

A thorough baseline screening will be followed for all patients and is outlined in Table-2. A detailed list of the methods in which baseline screening will be performed is outlined in Supplemental 2. All blood draws and safety assessments must be performed prior to study treatment administration. Appropriate safety assessments (e.g., evaluation of AEs and SAEs) should be repeated after dosing with study treatment. A physical examination, including general appearance and vital signs, will be performed as indicated in Table-2. If indicated, based on medical history and/or symptoms, additional exams will be performed at the discretion of the investigator. If possible, the same member of the study site staff throughout the study will perform assessments for an individual subject. Information for all physical examinations will be included in the source documentation at the study site. Significant findings that are present prior to the subject signing informed consent will be included in the Medical History. Significant findings made after the signing of the informed consent, which meet the definition of an AE, must be recorded as an AE. Vital signs (blood pressure, pulse, height, weight) will be assessed at each physical examination as indicated in Table-2 (see Supplemental 2 for details on how to acquire vital signs). Whether action needs to be taken to address notable vital signs will be decided by the investigator, considering the overall status of the subject. Laboratory studies will be drawn as indicated in Table-2. Whether action needs to be taken to address notable laboratory values will be decided by the investigator, considering the overall status of the subject. Hematology assessments will be measured at all scheduled study visits specified in Table-2. Serum chemistry will be a comprehensive metabolic panel will be measured at all scheduled study visits specified in Table-2.

If the prohibited treatment is being used during the study for any indication, the subject must discontinue use of the prohibited treatment if he/she wishes to continue in the study. In case of undue safety risk for the subject, the subject should discontinue study treatment at the discretion of the investigator/qualified site staff. If the subject received a live virus vaccination during the study, the subject must discontinue study treatment.

4.7 Identification of Source Data

All data in the study will be captured in the case report forms including:

- Safety measures
- Efficacy measures
- Laboratory studies
- Vital Signs
- Exploratory measures

5 Subject Selection Enrollment and Withdrawal

5.1 Inclusion Criteria

Subjects eligible for inclusion in this study must fulfill **all** the following criteria:

- Subjects must be able to understand and comply with the requirements of the study and communicate with the investigator. Subjects must give written, signed, and dated informed consent before any study related activity is performed. When appropriate, a legal representative will sign the informed consent according to local laws and regulation
- Both men and women must be at least 18 years of age at the time of screening
- Subjects must have clinical and histological features of LP
- LP up to 20% of the BSA
- Subjects must have a minimum of 4 lesions, ideally 10 lesions of LP
- Subjects must have treatment naïve cutaneous LP or treatment refractory disease, as defined by failure of at least one established treatment for LP
    - Failure of prior therapy
        - Topical treatment
        - Systemic immunosuppressant
        - Oral metronidazole
        - Oral sulfasalazine
        - Oral retinoid

5.2 Exclusion Criteria

Subjects fulfilling **any** of the following criteria are not eligible for inclusion in this study. To ensure the recruitment of a representative sample of all eligible subjects, the investigator may apply no additional exclusions.

- On excluded therapies, not on a stable dose of a therapy, or incompletely washed out for a therapy (Table-1.)
- Known hypersensitivity to any component of INCB018424 PHOSPHATE CREAM
- Variants of LP deemed by the investigators to be inappropriate for INCB018424 PHOSPHATE CREAM including by not limited to:
    - Erosive LP
    - Intertriginous LP
    - Oral LP
    - Facial LP

  - Drug-induced LP
  - Vaginal LP
- LP involving greater than 20% BSA
- Pregnant or nursing (lactating) women (pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test)
- Women of childbearing potential [Post-menopausal or not of child-bearing potential is defined by: 1 year of natural (spontaneous) amenorrhea or Surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks ago. Oophorectomy alone must be confirmed by follow up hormone level assessment to be considered not of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception which includes:
  - Total abstinence (Periodic abstinence and withdrawal are not acceptable methods of contraception)
  - Female sterilization (bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least 6 weeks before taking study treatment. Oophorectomy alone requires follow up hormone level assessment for fertility.
  - Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject.
  - Barrier methods of contraception: condom or occlusive cap.
  - Use of oral, injected or implanted hormonal methods of contraception or other forms or hormonal contraception that have complete efficacy (failure <1%). (The dose of the contraceptive should be stable for 3 months)
- Active ongoing inflammatory diseases of the skin other than LP that might confound the evaluation of the benefit of INCB018424 PHOSPHATE CREAM
- Underlying condition (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions) which, in the opinion of the investigator, significantly immunocompromised the subject and/or places the subject at unacceptable risk for receiving an immunomodulatory therapy
- Active systemic infections during the 2 weeks prior to randomization (common cold viruses not included) or any infection that reoccurs on a regular basis.
- Current severe progressive or uncontrolled disease which the investigator renders the subject unsuitable for the trial or puts the subject at increased risk

5.3 Subject Recruitment, Enrollment and Screening

- From the Principal Investigator or Co-Investigator clinical practices
- Screening requirements or qualifying lab values
- Evaluation and documentation of inclusion/exclusion criteria

5.4 Early Withdrawal of Subjects

5.4.1 When and How to Withdraw Subjects

- Subject safety issues

- Failure of subject to adhere to protocol requirements
- Disease progression
- Subject decision to withdraw from the study (withdrawal of consent)

Subjects who withdraw from the study for any reason will have their information recorded at the time of withdrawal. At the time of withdrawal, the subject will be considered at the final treatment date and will move into the treatment observation phase (4 weeks). Subjects will not be replaced. Follow up for subjects will continue to follow the normal follow up (Table-2)

5.4.2 Data Collection and Follow-up for Withdrawn Subjects

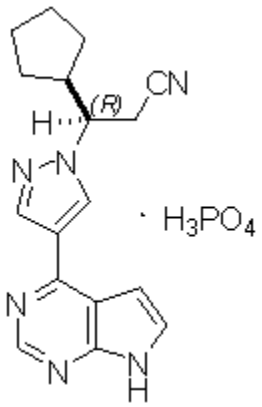
At the time of withdrawal, the reason for withdrawal will be recorded in the CRF. Individuals who withdraw will go into the observation phase for 4 weeks. If a subject withdraws consent, attempts will be made to obtain permissions to collect follow up information.

6 Study Drug

6.1 Description

The chemical name of INCB018424 phosphate is (R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate (Figure 1). INCB018424 phosphate has a molecular formula of C17H21N6O4P and a molecular weight of 404.36.

INCB018424 Phosphate Structural Formula



INCB018424 phosphate drug substance is a white to off-white to light pink powder. INCB018424 PHOSPHATE CREAM has been formulated in 4 strengths (0.15%, 0.5%, 1.0%, and 1.5% w/w free base equivalent) that are actively being investigated. All excipients in both the INCB018424 PHOSPHATE CREAM and placebo cream formulations are compendial grade or are approved for use in topical products.

INCB018424 PHOSPHATE CREAM is a topical formulation of an investigational product under development for the treatment of patients with psoriasis, alopecia areata, atopic dermatitis, and other potential autoimmune diseases of the skin. INCB018424 phosphate (ruxolitinib) is an inhibitor of the Janus kinase (JAK) family of protein tyrosine kinases. INCB018424 inhibits Janus Associated Kinases (JAKs) JAK1 and JAK2 which mediate the signaling of a number of

cytokines and growth factors that are important for hematopoiesis and immune function. JAK signaling involves recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, activation and subsequent localization of STATs to the nucleus leading to modulation of gene expression. Mitogenic and inflammatory cytokines are strongly implicated in the pathogenesis of psoriasis, alopecia areata, atopic dermatitis, and other potential autoimmune diseases of the skin. Inhibition of specific cytokine function using antibodies directed against the common p40 subunit of interleukin (IL)-12 and IL-23 has demonstrated proof-of-concept validating cytokine signaling as a therapeutic target for the treatment of psoriasis.

INCB018424 PHOSPHATE CREAM has been evaluated in over 200 subjects in 3 clinical studies with dosing of 1 to 3 months in duration. One study of 12 subjects with Alopecia Areata.

Pharmacodynamics:
Ex vivo addition of INCB018424 to the whole blood samples from psoriasis subjects inhibited cytokine-induced STAT3p levels with a similar potency to that observed previously in whole blood from healthy volunteers (IC50 = 334 nM vs 414 nM, respectively). No significant inhibition of mean systemic STAT3p was observed in any cohort following topical INCB018424 application.

Pharmacokinetics:
Study 1:
• Cohort A: INCB018424 PHOSPHATE CREAM 0.5% versus vehicle applied QD.
• Cohort B: INCB018424 PHOSPHATE CREAM 1.0% versus vehicle applied QD.
• Cohort C: INCB018424 PHOSPHATE CREAM 1.5% versus vehicle applied BID.

Application of INCB018424 PHOSPHATE CREAM 0.5% to 1.5% QD or BID resulted in mean plasma concentrations of INCB018424 ranging from 0.34 ± 0.4 nM (Cohort A) through 2.10 ± 1.78 nM (Cohort C) at steady state. The mean INCB018424 steady-state concentration increased approximately proportional to application dose per day. The size of the lesion areas treated ranged from 9 to 63 cm2. Application of INCB018424 PHOSPHATE CREAM 0.5% to 1.5% QD or BID resulted in a mean skin flux of INCB018424 ranging from 54 ± 41 ng/cm2/h (Cohort A) through 422 ± 200 ng/cm2/h (Cohort C). The mean skin flux of INCB018424 increased with increasing application (API) strength. The mean systemic bioavailability was 2.8 ± 3.2%, 3.0 ± 1.9%, 3.0 ± 1.9%, 2.7 ± 1.1%, and 2.7 ± 2.3% for Cohorts A through E, respectively. The systemic bioavailability of INCB018424 applied as a topical cream appears independent of the strength of the cream formulation.

Study 2:
• Cohort A: treat 2%-7% BSA with 1.5% BID in 5 subjects
• Cohort B: treat 8%-13% BSA with 1.5% BID in 5 subjects
• Cohort C: treat 14%-20% BSA with 1.5% QD in 5 subjects
• Cohort D (optional): treat 14%-20% of BSA with 1.0% QD or BID in 5 subjects
• Cohort E (optional): treat 14%-20% of BSA with 1.5% QD or BID in 5 subjects

The average plasma concentrations of INCB018424 for Cohort A , Cohort B, Cohort C, Cohort D, and Cohort E were 7.00 ± 2.11 nM, 29.38 ± 13.10 nM, 24.42 ± 10.07 nM, 34.96 ± 20.43 nM,

and 60.99 ± 73.85 nM, respectively, at the steady state. The mean INCB018424 Css increased approximately proportional to application dose per day. The mean skin flux of INCB018424 was estimated to be 180 ± 126 ng/cm2/h, 131 ± 92 ng/cm2/h, 60 ± 43 ng/cm2/h, 151 ± 126 ng/cm2/h, and 152 ± 74 ng/cm2/h, respectively, for Cohorts A, B, C, D, and E. The mean topical bioavailability was estimated to be 3.8 ± 2.5%, 4.1 ± 3.4%, 3.4 ± 1.9%, 3.9 ± 1.3%, and 5.2 ± 1.9%, respectively, for Cohorts A, B, C, D, and E. Based on this result, it is concluded that the systemic bioavailability of INCB018424 applied as a topical cream is independent of the strength of the cream formulation and %BSA.

Study 3:
• Treatment A: INCB018424 PHOSPHATE CREAM 0.5% applied QD for 12 weeks
• Treatment B: INCB018424 PHOSPHATE CREAM 1.0% applied QD for 12 weeks
• Treatment C: INCB018424 PHOSPHATE CREAM 1.5% applied QD for 12 weeks
• Treatment D: Vehicle containing placebo cream applied QD for 12 weeks

Application of INCB018424 PHOSPHATE CREAM 0.5%, 1.0%, and 1.5% QD resulted in mean steady-state trough plasma concentrations (Css,min) of INCB018424 of 9.19 ± 11.77 nM, 16.99 ± 19.05 nM, and 19.97 ± 25.13 nM, respectively, for 0.5% QD to 1.5% QD. Thus, the mean INCB018424 Css,min increased approximately proportional to application dose. As the severity of lesion thickness, erythema, and scale increased, the INCB018424 Css,min appeared to be decreased for the same treatment. The subjects with less severe lesion thickness, erythema, and scale seemed to have higher trough INCB018424 exposures.

Study 4:
Twelve subjects were enrolled in Part A (1.5% BID). Pharmacokinetic data were available for 12 subjects at Week 4 and 5 subjects at Week 12. Application of INCB018424 PHOSPHATE CREAM 1.5% BID resulted in mean steady state plasma concentrations of 25.4 ± 15.9 nM at Week 4 and 43.0 ± 36.5 nM at Week 12, which are generally consistent with the steady state concentrations seen in subjects with psoriasis. Steady state was assumed to be achieved at Day 8.

6.2 Treatment Regimen

Subjects will apply the study drug topically to LP lesions twice daily. Treatment will take place from Day 0 to Week 8.

6.3 Preparation and Administration of Study Drug

The study drug will be supplied by Incyte to the Mayo Clinic Pharmacy, attn. [redacted], [redacted], Scottsdale, AZ [redacted]. The study drug will be stored in the Mayo Clinic Pharmacy. The study drug will be labelled in the Mayo Clinic Pharmacy and will be dispensed to the subjects. The subjects will be given the appropriate amount of topical cream to apply to the disease. Instructions on proper use will be provided to each subject.

6.4 Subject Compliance Monitoring

Compliance will be assessed through direct questioning of subjects as well as through drug use diaries. The drug tubes will be weighed, and weight will be documented at each visit to determine usage.

6.5 Prior and Concomitant Therapy

Individuals on stable doses of medications for chronic illnesses will be allowed. Individuals on immunosuppressive agents for LP will not be allowed; however, individuals on stable doses of immunosuppressant for other conditions will be allowed if deemed to be safe by the treating physicians. Additional exclusionary drugs are included in Table-1.

Individuals using INCB018424 PHOSPHATE CREAM should use topical broad spectrum sunscreens with a minimum of SPF30, avoid excess sunlight, and wear sun protective clothing.

6.6 Packaging

The drug will be packaged in 15 gram single tubes and bubble wrapped for shipment. The entire quantity needed for the study will be provided in one shipment. The study drug tubes will be labeled with a diaper label that fully surrounds the tube. All applicable US FDA required text will be included on the label, included Caution: Limited by U.S. Law to Investigational Use

6.7 Receiving, Storage, Dispensing and Return

6.7.1 Receipt of Drug Supplies

The drug will be obtained or delivered from Incyte Corporation to the pharmacy at each investigative site.

Upon receipt of the of the study treatment supplies, an inventory must be performed and a drug receipt log filled out by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipping invoice. Any discrepancies, damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The sponsor-investigator must be notified immediately of any discrepancies, damaged or unusable products that are received.

6.7.2 Storage

The INCB018424 PHOSPHATE CREAM drug product and placebo cream should be stored between 15°C and 30°C (59°F and 86°F). The supplies will be stored in the Mayo Clinic Pharmacy.

6.7.3 Dispensing of Study Drug

Regular study drug reconciliation will be performed to document drug assigned, drug dispensed, drug returns, and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the study team.

6.7.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug dispensed, drug returns, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be documented and investigated, prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

7 Study Procedures

7.1 Visit 1

Screening visit:

During this visit, we will do some tests and procedures to see if subjects are eligible to take part in this research study. The study staff will review the results of these tests and procedures. If subjects aren't eligible, the Principal Investigator will tell them why. At this visit we will:

- Ask about medical history
- Perform a physical exam, including height, weight, and "vital signs" (blood pressure, temperature, heart and breathing rates)
- Perform a chest x-ray
- Draw a blood sample
- We may take swabs to test for certain fungal and bacterial infections
- Test urine for pregnancy if female subject is able to become pregnant

If it isn't known if subject has HIV, Hepatitis B or C, blood tests will need to be done.

7.2 Visit 2

Day 0 Visit we will:

- Perform a physical exam, check vital signs and ask about side effects or health problems since last visit
- Exam skin lesions to note any changes
- Take photographs of skin lesions to document any changes
- Draw a blood sample
- Perform a skin biopsy (up to 3 tissue samples will be taken)
- Perform a tap stripping on skin
- Dispense study drug

7.3 Visit 3

Week 1 Visit we will:

- Perform a physical exam, check vital signs and ask about side effects or health problems since last visit
- Exam skin lesions to note any changes
- Take photographs of skin lesions to document any changes
- Draw a blood sample
- Dispense study drug

7.4 Visit 4

Week 2 Visit we will:

- Perform a physical exam, check vital signs and ask about side effects or health problems since last visit
- Exam skin lesions to note any changes
- Take photographs of skin lesions to document any changes
- Draw a blood sample
- Dispense study drug

7.5 Visit 5

Week 3 Visit we will:

- Give subject a physical exam, check vital signs and ask about side effects or health problems since last visit
- Exam skin lesions to note any changes
- Take photographs of skin lesions to document any changes
- Draw a blood sample
- Dispense study drug

7.6 Visit 6

Week 4 Visit we will:

- Perform a physical exam, check vital signs and ask about side effects or health problems since last visit
- Exam skin lesions to note any changes
- Take photographs of skin lesions to document any changes
- Draw a blood sample
- Perform a skin biopsy (up to 2 tissue samples will be taken)
- Perform a tap stripping on skin
- Dispense study drug

7.7 Visit 7

Week 8 Visit we will:

- Perform a physical exam, check vital signs and ask about side effects or health problems since last visit
- Exam skin lesions to note any changes
- Take photographs of skin lesions to document any changes
- Draw a blood sample

7.8 Visit 8

Week 12 Visit we will:

- Perform a physical exam, check vital signs and ask about side effects or health problems since last visit
- Exam skin lesions to note any changes
- Take photographs of skin lesions to document any changes
- Draw a blood sample

8 Statistical Plan

8.1 Sample Size Determination

Data analysis: Assuming a medium effect size (0.3) and a target power of 80%, a two-armed study would need about 108 subjects and a single arm about 88 subjects. Due to the costs associated with a study, we propose a single armed study of 12 subjects with corollary science including RNA sequencing. This will reduce costs and provide biomarkers predictive of response. Effect sizes will be estimated for the appropriate statistical tests that will be used for group comparisons in future studies. This will enable more accurate power and sample size estimates moving forward.

8.2 Statistical Methods

Descriptive Statistics

Sample Size Computation and Power Analysis:
The sample size for this pilot study is set at 12 subjects for logistical and financial reasons. This is similar in size to other exploratory studies and will provide adequate data for estimation purposes for planning future studies. With 12 subjects, the study is intended to be for estimation purposes only.

Statistical Analysis Plan:
Data Analysis - The statistical analysis will provide descriptive summary statistics for categorical and continuous outcomes. Categorical variables will be described by their count and proportion of occurrence while continuous, normally distributed variables will be described by their mean and standard deviation; and continuous, non-normally distributed variables will be described by their median and range. The paired or unpaired Wilcoxon tests will be used to quantify differences in numerical outcomes while the Fisher's exact test and the McNemar's or Bowker's tests will be used to quantify changes in categorical variables.
If missingness occurs at random a mixed model will be utilized to assess the change in the lesion over time. A sensitivity analysis will be performed using the last observation carried forward and the results will be compared to that of the mixed-model.
Effect sizes will be estimated for the appropriate statistical tests that will be used for group comparisons in future studies. This will enable more accurate power and sample size estimates moving forward.

Bioinformatic Analysis:
RNA-seq analysis: We will use our recently developed LinNorm program (https://www.bioconductor.org/packages/release/bioc/html/Linnorm.html) to process RNA-seq data and detect differentially expressed genes (DEGs) by comparing the RNA-seq profiles. We will first find DEG between responsive and non-responsive samples from the same individual by using paired or unpaired Wilcoxon rank-sum test (depending on how the samples are collected). We will then rank each gene in the DEGs based on the occurrence frequencies in all 12 subjects

to find common DEGs for responsiveness (use permutation test to determine the p value). For the top ranked genes (common DEGs), we will use DAVID (3) and GSEA (4) software to find enriched inflammatory pathways and GO terms for the DEGs. By comparing the normal tissue with the pathogenic tissue (responsive + non-responsible) using the above approach, we will detect a common DEGs for LP pathogenesis. Hierarchical clustering (5) and Principal Component Analysis (PCA) (6) will be applied to samples for their hierarchical relationship and clustering properties. Ideally normal, responsive and non-responsible tissues should form three distinct groups. The PCA analysis will provide us a set of gene signatures that can distinguish these three types of tissues. The common DEGs for responsiveness and pathogenesis, as well as gene signature from PCA will be used for our pathogenesis or survival prediction. We will perform structure variants calling from RNA-seq data with SNPiR (7), and reconstruct gene co-expression networks with ARACHNE.(8) Additionally, we will perform de-convolutional analysis, to compare the immune profiles of responsive and non-responsive tissue and to correlate immune profiles. Predictive biomarkers will be correlated with lesional and global responses.

8.3 Subject Population(s) for Analysis

- All-completed population: All subjects that receive at least one dose will be considered for analysis.

9 Safety and Adverse Events

9.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)
Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event
An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event
Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant disability or incapacity
- birth defect/anomaly

and/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

Adverse Event Reporting Period

For this study, the study treatment follow-up period is defined as 30 days following the last administration of study treatment.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

A thorough baseline screening will be followed for all subjects and is outlined in Table-2. A detailed list of the methods in which baseline screening will be performed is outlined in Supplemental 2. All blood draws and safety assessments must be performed **prior** to study treatment administration. Appropriate safety assessments (e.g., evaluation of AEs and SAEs) should be repeated after dosing with study treatment. A physical examination, including general appearance and vital signs, will be performed as indicated in Table-2. If indicated, based on medical history and/or symptoms, additional exams will be performed at the discretion of the investigator. If possible, the same member of the study site staff throughout the study will perform assessments for an individual subject. Information for all physical examinations will be included in the source documentation at the study site. Significant findings that are present prior to the subject signing informed consent will be included in the Medical History. Significant findings made after the signing of the informed consent, which meet the definition of an AE, must be recorded as an AE. Vital signs (blood pressure, pulse, height, weight) will be assessed at each physical examination as indicated in Table-2 (see Supplemental 2 for details on how to acquire vital signs). Whether action needs to be taken to address notable vital signs will be decided by the investigator, considering the overall status of the subject.

Supplemental 1: Appropriateness of Measures

Skin Scoring:
There are no validated skin scoring systems for LP. Therefore, we will use simple measures of BSA which is objective and PGA which is well validated in other inflammatory skin conditions. Additionally, we will simply annotate the number of lesions on the individual as a marker of total disease burden. The later measure, CAILS was devised for evaluation of cutaneous T-cell lymphoma lesions for trial purposes. This system provides accurate measurements of CTCL patches, plaques, and tumors. This scoring system captures lesion redness, size, texture,

pigmentation and elevation characteristics. We will use a Modified CAILS scoring system that discards pigmentation scoring as resolving LP lesion inherently leave behind hyperpigmented skin changes which may confound active lesion scoring. This will provide a composite analysis of the index lesions as well as the general body involvement of the individual. The Modified CAILS system is advantageous over the PASI or EASI system in that in allows for more accurate calculation of surface area and incorporates that into the final score.

In cases where some or all of the affected body regions contain such extensive LP disease that make counting individual LP lesions unfeasible, the lesion count in these areas will be estimated. The palmar surface of the hand equates to approximately 1% BSA. To estimate the lesion count in a body region of extensive disease, the number of lesions counted within an area equivalent to area the palmar surface of the hand within that extensively diseased body region will be multiplied by the representative BSA of that body region to determine the estimated lesion count contained in that body region. Representative BSAs of body regions are defined as follows: head (7%), neck (2%), anterior trunk (13%), arms (8%), forearms (6%), hands (5%), posterior trunk (13%), buttocks (5%), thighs (19%), legs (14%), feet (7%) and groin (1%).

Itch Scoring:

The NRS and Skindex-16 are all well validated measure of itch. The First score measure focuses in upon a gestalt of itch. The later scoring system focuses in upon the itch and its impact upon quality of life.

Supplemental 2: Safety Measures

Baseline Screening:

A serum β-hCG test will be performed in all pre-menopausal women as indicated. All pre-menopausal women who are not sterile at screening will also have a urine pregnancy test performed locally as indicated. Any woman with a confirmed positive pregnancy test during screening is not eligible for the study. A positive urine pregnancy test during the treatment periods of the study requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative. If the serum β-hCG test is positive, study treatment must be definitively discontinued.

Blood Pressure and Pulse:

Height and Weight:
Height and body weight will be measured in indoor clothing, but without shoes. If possible, body weight assessments should be performed by the same study site staff member and using the same scale throughout the study.

Blood Draws:
Subjects should avoid smoking within the hour preceding the blood draws. All laboratory studies will be conducted within the Mayo Clinic Health Systems (Mayo Clinic Arizona and Mayo Clinic Rochester). Details on the collections, shipment of samples and reporting of results will follow

Mayo Clinic's current protocols. For the identification of notable values, the Mayo Clinic reference laboratory should be consulted.

Supplemental 3: Safety Monitoring

Infection monitoring:
Study subjects will be evaluated at each visit for signs or symptoms of infection.

- Vitals signs as well as constitutional symptoms will be assessed.
- Assessment for common infections such as cellulitis as well as oral, vaginal, and cutaneous candidiasis will be performed

Post-study Adverse Event
All unresolved adverse events should be followed by the sponsor-investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the sponsor-investigator should instruct each subject to report, to the sponsor-investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Laboratory studies will be drawn as indicated in Table-2. Whether action needs to be taken to address notable laboratory values will be decided by the investigator, considering the overall status of the subject. Hematology assessments will be measured at all scheduled study visits specified in Table-2. Serum chemistry will be a comprehensive metabolic panel will be measured at all scheduled study visits specified in Table-2.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

9.2 Recording of Adverse Events

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should recorded in the source document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs during the Adverse Event Reporting Period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

9.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

9.3.1 Sponsor-Investigator reporting: notifying the Mayo IRB

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

Action taken regarding treatment

AE Action:
All adverse events should be treated appropriately. Treatment may include one or more of the following:

- No action taken (i.e. further observation only)
- [study/investigational] treatment dosage adjusted/temporarily interrupted
- [study/investigational] treatment permanently discontinued due to this adverse event
- concomitant medication given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged

AE Outcome:

- All AE outcomes should be recorded (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Serious Adverse Events (SAE)

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria (Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.):

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

SAE Reporting:

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30-days after the subject stopped study participation must be reported to the Incyte as soon as possible but no later than 5 days from learning of its occurrence according to the Mayo Clinic IRB policy. Any SAEs experienced after the 30-days period should only be reported to Incyte and the Mayo Clinic IRB if the investigator suspects a causal relationship to study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted as soon as possible but no later than 5 days from the investigator receiving the follow-up information. SAE should be followed up until resolution or until it is judged to be permanent. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information collected on the adverse event worksheet (*and entered in the research database)*:

- Subject's name:
- Medical record number:
- Disease/histology (if applicable):
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research (drug, procedure, or intervention*):
- If the adverse event was expected:
- The severity of the adverse event: (use a table to define severity scale 1-5**)
- If any intervention was necessary:

- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

AE Reporting:
Its relationship to the:
- Study treatment (no/yes), or
- Investigational treatment (no/yes), or
- The other study treatment (non-investigational) (no/yes), or
- Both or indistinguishable

The relationship will be categorized as follows:
- Unrelated- Clearly due only to extraneous causes, and does not meet criteria listed under possible or probable.
- Unlikely- Does not follow a reasonable temporal sequence from administration. May have been produced by the patient's clinical state or by environmental factors or other therapies administered.
- Possible- Follows a reasonable temporal sequence from administration, but may have been also produced by the patient's clinical state, environmental factors or other therapies administered.
- Probable- Clear-cut temporal association with administration with improvement on cessation of investigational medicinal product or reduction in dose. Reappears upon rechallenge. Follows a known pattern of response to the investigational medicinal product.

Its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
Whether it constitutes a serious adverse event(SAE)

Adverse Events (AE):
The severity grade/Common Toxicity Criteria (CTC) AE Version 4.0 grade
- Mild: usually transient in nature and generally not interfering with normal activities
- Moderate: sufficiently discomforting to interfere with normal activities
- Severe: prevents normal activities

If CTCAE grading does not exist for an adverse event, use
1=mild, 2=moderate, 3=severe, 4=life-threatening, CTCAE Grade 5 (death) is not used, but is collected in other CRFs (Study Completion, Death/Survival).

9.3.2 Sponsor-Investigator reporting: Notifying the FDA and Funding Sponsor

The sponsor-investigator will report to the FDA all unexpected, serious suspected adverse reactions according to the required IND Safety Reporting timelines, formats and requirements.

Unexpected fatal or life threatening suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than 7 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Other unexpected serious suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than 15 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Any clinically important increase in the rate of serious suspected adverse reactions over those listed in the protocol or product insert will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A no later than 15 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Findings from other studies in human or animals that suggest a significant risk in humans exposed to the drug will be reported. This will be reported to the FDA on FDA Form 3500A, no later than 15 calendar days after the sponsor-investigators initial receipt of the information about the event.

SAE Reporting to the Sponsor (Incyte)

All Serious Adverse Events ("SAE") required to be reported pursuant to the Protocol shall be provided to Incyte and its representatives by Institution or Principal Investigator within twenty-four (24) hours of learning of the event as well as provide any additional reports agreed upon by the Institution or Principal Investigator and Incyte's contact below. SAE Reports will be sent to the email address provided below. By sending to this e-mail address, the Incyte Pharmacovigilance group and the Incyte clinical operations project manager will receive copies of the reports. This process will be tested and established before the first patient is enrolled in the trial. Notwithstanding anything to the contrary herein, Institution or Principal Investigator will have the primary responsibility of reporting adverse events ("AE") to regulatory authorities.

Copies of IND safety reports submitted to the FDA by the Institution will be shared with the contact below so that these reports can be evaluated and included in investigator brochure or Incyte IND safety submissions as required to ensure safety of other patients who are receiving the product from Incyte for sponsored trials.

Incyte Corporation: [redacted] for e-mail transmission of individual SAE reports.

Safety Contacts: [redacted], Exec. Dir, Incyte Pharmacovigilance, Phone: [redacted] Email: [redacted]

Procedure for Reporting of Pregnancy and Lactation to the Sponsor (Incyte)

Data on fetal outcome are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Within 30 days of learning of the pregnancy, the investigational site completes the Clinical Trial Pregnancy Form (sections I, II, and question 18 in section III) or equivalent, and e-mails the report to Incyte at [redacted]

Within 30 days of learning of the outcome of the pregnancy (delivery, termination, or miscarriage), the investigational site completes the Clinical Trial Pregnancy Form (sections II, III, IV, and V) or equivalent, and e-mails the report to Incyte at [redacted]
NOTE: If a woman has a positive pregnancy test at Baseline, the investigational site completes Clinical Trial Pregnancy Form (sections I, II, and III (question 18)) or equivalent and e-mails the report to Incyte at [redacted] as per established timelines.

Any SAE occurring during pregnancy must be reported to Incyte as an SAE, in accordance with Section 3 of the Serious Adverse Event Reporting Plan, as provided by Incyte.

9.4 Stopping Rules

The stopping rules specified below are based on the knowledge available at study development. The stopping rule applies to the overall study. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as “possible”, “probable”, or “definite”) that satisfy the following:

• If 2 or more patients in the first 6 treated patients (or 30% after the first 6 treated patients have been accrued) experience a grade 3 or higher non-hematologic adverse event.

We note that we will review grade 4 and 5 adverse events deemed “unrelated” or “unlikely to be related”, to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

9.5 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 “Study Monitoring, Auditing, and Inspecting”). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

The occurrence of adverse events will be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when the patient volunteers them

during or between visits or through physical examination, laboratory test, or other assessments. Please see Supplemental 3 for a detailed description of safety monitoring. Clinically significant abnormal laboratory values or test results will be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for labs and other test abnormalities are included determined by the Mayo Clinic Arizona and Mayo Medical Laboratory. Adverse events will be recorded in the Adverse Events Case Report Form (CRF) under the signs, symptoms or diagnosis associated with them, and severity. All adverse events will be treated appropriately. Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome (see Supplemental 3). Information about common side effects already known about the investigational drug can be found in the package insert. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. The investigator will also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents, however, if the AE meets the criteria of an SAE. To ensure patient safety, every SAE (see Supplemental 3 for definition), regardless of suspected causality, occurring after the patient has provided informed consent and after the patient begins taking study drug and until 30 days after the patient has stopped study participation will be recorded and reported to Incyte. Any SAEs experienced after this 30-day period should only be reported to Incyte if the investigator suspects a causal relationship to the study drug. All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met. Medical and scientific judgment will be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the outcomes listed in SAE. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction. All AEs (serious and non-serious) are captured and recorded, SAEs also require individual reporting (see Supplemental 3). To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to the sponsor-investigator within 24 hours of learning of its occurrence. The pregnancy should be followed up 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. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment. Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

10 Data Handling and Record Keeping

10.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information

The rights of a research subject to revoke their authorization for use of their PHI. *(This information is contained within the Mayo IRB Informed Consent Template Sectio*Study data will be securely stored on a password protected computer that only the research study team will have access to. Any study related paper documents will be stored in a locked cabinet that only the research study team will have access to.

- *14)*

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

10.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

10.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

Data Security and Confidentiality

All study data will be collected by the research team, reviewed by the PI, and stored in secure, locked files and/or databases in order to protect it from inadvertent loss or improper access. All laboratory specimens, evaluation forms, reports, and other records will be identified by coded number only to maintain subject confidentiality. Information gained from this study that can be linked to the subject's identity will not be released to anyone other than the investigators, the subject and the subject's physician. All the information obtained in connection with these studies will remain confidential as far as possible within state and federal law. The results of these studies will be published in scientific journals without identifying the subjects by name.

Data Quality Assurance

Source document verification will be performed to ensure that the database accurately reflects data on the CRFs.

Data Clarification Process

10.4 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents. These will include subject case histories and regulatory documents. There will be a subject code master list that will be stored so as to protect subjects'confidentiality. Case Report Forms will be coded. There will be no subject names or other directly identifiable information will not appear on any reports, publications, or other disclosures of clinical study outcomes.

The sponsor-investigator will retain the specified records and reports for;

1. Up to 2 years after the marketing application is approved for the drug; or, if a marketing application is not submitted or approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been so notified. OR
2. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" [redacted]

Whichever is longer

11 Study Monitoring, Auditing, and Inspecting

11.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

11.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

12 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

13 Study Finances

13.1 Funding Source

Incyte Corporation is funding this research study.

13.2 Subject Stipends or Payments

Subjects will receive $50 for each biopsy visit they complete (Day 0 and Wk4). They will receive $25 for all other visits that they complete. If they complete all study visits they will receive a total of $250.

14 Publication Plan

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results

of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

15 References

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16 Attachments

Appendix:

Physician Global Assessment: (9, 10)
Grade 0 Completely clear: no evidence of disease (100% improvement) CCR
Grade 1 Almost clear: very significant clearance (≥90% to <100%) PR
Grade 2 Marked Improvement: significant improvement (≥75% to <90%)PR
Grade 3 Moderate improvement: intermediate between slight and marked (≥50% to <75%) PR
Grade 4 Slight improvement: some improvement (≥25% to <50%); however, significant evidence of disease remains SD
Grade 5 No change; disease has not changed from baseline condition (+/-<25%) SD
Grade 6 Worse, disease is worse than at baseline evaluation by (≥25%) or more PD

CCR- Complete clinical response
PR- Partial response
SD- Stable disease
PD- Progressive Disease

Modified CAILS-
Clinical Assessment Scale of Severity for Index Lesion Signs and Symptoms (CAILS) (9, 10)

Scale	Grade
0	No evidence of sign or symptom
1	Intermediate interval
2	Mild: less than average presentation of sign or symptom
3	Intermediate interval
4	Moderate: average disease presentation of sign or symptom
5	Intermediate interval
6	Severe: greater than 25% worse than average severity of sign or symptom
7	Intermediate interval
8	Very severe: the near worst severity sign or symptom

A scale of 0 to 18 was used to grade lesion size by square centimeter (0, 0 [no measurable area]; 1, >0 and ≤4; 2, >4 and ≤10; 3, >10 and ≤16; 4, >16 and ≤25; 5, >25 and ≤35; 6, >35 and ≤45; 7, >45 and ≤55; 8, >55 and ≤70; 9, >70 and ≤90; 10, >90 and ≤110; 11, >110 and ≤130; 12, >130 and ≤155; 13, >155 and ≤180; 14, >180 and ≤210; 15, >210 and ≤240; 16, >240 and ≤270; 17, >270 and ≤300; and 18, >300). The area of the lesion will be measured with digital planimetry. (9-11)

Modified CAILS index lesion score:
1. Erythema(0-8)
2. Scaling (0-8)
3. Plaque elevation (0-8)
4. Size (0-18)

o Trained clinical evaluators assessed the same patients throughout the study.
o The CA (the ratio of summation (Σ) of all clinical signs for these index lesion at each visit compared with baseline) included cutaneous tumors and all extra cutaneous manifestations of disease.
o Complete clinical remission (CCR) required a CA ratio of 0 with no evidence of disease
o Partial remission (PR) was defined as
o A CA ratio of 0.5 or lower without new clinically abnormal lymph nodes
o Progressive disease was defined as
o A 25% or higher increase in CA ratio
(Olsen et al., 2011b, Duvic et al., 2001b)

Itch-
Numerical Rating Scale (NRS) (bottom)- (12, 13)

0- No itch
1-4 Mild itch
4-7 Moderate itch
7-9 Severe itch
10- Very severe itch

Skindex-16-

Skindex 16 (14, 15)-

Scoring (0=never bothered to 6=always bothered), Total 0 to 96

Symptom Subscale
1. Skin itching
2. Skin burning or stinging
3. Skin hurting
4. Skin irritated

Emotional Subscale
5. Persistence or recurrence of condition
6. Worry about condition
7. Appearance of skin
8. Frustration about skin
9. Embarrassment about skin
10. Annoyed about skin
11. Feeling depressed

Functional Subscale
12. Effect of skin on interaction with others
13. Effect of skin on desire to be with people
14. Skin making it hard to show affection
15. Effect of skin on daily activity
16. Skin making it hard to work/have enjoyment