Deucravacitinib (BMS-986165) in the Treatment of Lichen Planopilaris

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Regulatory Sponsor:	Aaron Mangold, MD
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Study Product:	Deucravacitinib (BMS-986165) oral medication
Protocol Number: (IRBe)	IRB 23-001929 (BMS Protocol Number – IM011-1173)
IND Number:	Exempt
Protocol Version 1.6	10.29.24

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
BSA	Body Surface Area
mCAILS	Modified 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
LPPAI	Lichen Planopilaris Activity Index
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
VAS	Visual Analogue Score
VRS	Visual Rating Score

Study Summary

Title	**Deucravacitinib (BMS-986165) in the Treatment of Lichen Planopilaris**
Running Title	Deucravacitinib (BMS-986165) in LPP
Protocol Number	Version 1.6
Phase	2
Methodology	Open-Label, Single Arm
Overall Study Duration	28 weeks
Subject Participation Duration	Up to 28 weeks
Single or Multi-Site	Single institution (MCA and MCF participating)
Objectives	To evaluate the safety and efficacy of Deucravacitinib (BMS-986165) in Lichen Planopilaris and Frontal Fibrosing Alopecia as assessed by the change in Physician Global Assessment (PGA) of skin, oral mucosa, and hair, LPPAI. To predict responses through the identification of unique biomarkers of LPP at week 0 and utilizing bulk, spatial, and single-cell RNA sequencing
Number of Subjects	22 (12 in cohort A and 10 in cohort B)
Diagnosis and Main Inclusion Criteria	Adult patients with active LPP 1) 18 years old or older at time of consent 2) Biopsy proven diagnosis of LPP
Study Product, Dose, Route, Regimen	Deucravacitinib (BMS-986165) 6 mg orally administrated, twice daily (Cohort A) and 6 mg orally QD (Cohort B).
Duration of Administration	Drug will be administered from Day 0 through Week 24.
Reference therapy	None
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.

1 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.

1.1 Background

Deucravacitinib (BMS-986165) is an oral selective inhibitor of tyrosin kinase 2 (TYK2), a member of the Janus kinase (JAK) family. Deucravacitinib (BMS-986165) binds to the regulatory domain of TYK2 (also known as pseudokinase domain) to stabilize an inhibitory interaction between the regulatory and the catalytic

domains of the enzyme. This results in allosteric inhibition of receptor-mediated activation of TYK2 and its downstream activation of Signal Transducers and Activators of Transcription (STATs). JAK kinases, including TYK2, function as pairs of homo- or heterodimers in the JAK-STAT pathways. TYK2 activates STAT-dependent gene expression and functional responses of interleukin (IL)-12, IL-23, and type I interferon (IFN) receptors. IL-12 promotes Th1 differentiation in T-cells and enhances the production of IFN gamma [1]. IL-23 is an inflammatory cytokine that stimulates development and differentiation of Th17 cells via activation on STAT3. Subsequently, Th17 cells secrete inflammatory mediators, including IL-17 and TNF-alpha [2]. IL-23 also exerts its effects on dendritic cells and macrophages to stimulate production of IL-1, IL-6, and TNF-alpha.

Deucravacitinib (BMS-986165) represents a therapeutically attractive drug by inhibiting these cytokine pathways. This study is aimed at evaluating the effects of Deucravacitinib (BMS-986165) 6 mg twice daily (Cohort A) in subjects with Lichen Planopilaris (LPP). Our preliminary results of Deucravacitinib (BMS-986165) 6mg BID (Cohort A) improved disease activity by the LPPAI and PGA at weeks 12 and 16. In addition, clinical signs and symptoms were improved at 3-4 months and was well tolerated.

Lichen Planopilaris (LPP) is a form of lymphocyte-mediated scarring alopecia. It presents as discrete patches with characteristic perifollicular erythema and scale involving the scalp. LPP is histopathologically characterized by lichenoid inflammation at the infundibular portion of hair follicle. Cell-mediated cytotoxicity is the main pathogenetic mechanism in lichenoid tissue reactions and the maintenance and progression of chronic cytotoxic inflammation requires IFN gamma signaling. Disease progression results in permanent alopecia and is associated with negative quality of life impacts including depression and anxiety. There are no on-label or effective remittive treatments. Conventional topical (e.g. corticosteroids) and systemic immunosuppressives (e.g. mycophenolate mofetil) used in the treatment of LPP directly inhibit lymphocytes but generally cannot induce clinical remission [3]. Therefore, there remains a critical unmet need for alternative therapeutic options to treat LPP.

Cutaneous LP is characterized by Type I and Type II IFN driven cell mediated cytotoxic immune response that is highly responsive to JAK1, 2 inhibitions [4-6]. However, unlike LP, LPP is a chronic, scarring condition. The etiology of LPP as well as the scarring is poorly understood; however, Th17 cells are thought to play a critical role in this process. In line with the role of Type I & II IFNs and Th17 cells in LPP, more moderate responses are seen with to JAK 1, 2 inhibition [7 8,9]. Taken together, we believe that TYK2 inhibition has the potential to treat the inflammation of LPP as well as the scarring generated by Th17 stimulated fibroblasts.

We additionally propose a multi-center, exploratory, open-label, single-arm design study using Deucravacitinib (BMS-986165, systemic TYK2 inhibitor for the treatment of LPP with 6 mg orally QD (Cohort B) to assess safety and efficacy.

1.2 Investigational Agent

Deucravaticinib (BMS-986165) is an oral agent that selectively inhibits TYK2 via allosteric mechanism. TYK2 mediates the signaling of inflammatory cytokines of adaptive (IL-12, IL-23) and innate (type I IFN) immune responses. Inhibition of TYK2 leads to the downregulation of the IL-23/Th17 pathway, IL-12 signaling, and type I IFN pathway. Type I & II IFNs and Th17 cytokines play a key role in the pathogenesis of LPP.

1.3 Preclinical Data

All preclinical data below is referenced from the IB. Please refer to the IB for more details.

1.4 Clinical Data to Date

Clinical data to date is referenced from the IB. Please refer to the IB for more details.

1.5 Dose Rationale

Balancing the safety risks and efficacy data of varying Deucravacitinib (BMS-986165) doses from prior studies, our study proposes oral Deucravacitinib (BMS-986165) 6 mg BID (Cohort A) and 6mg QD (Cohort B) dosing for 24 weeks (primary endpoint) in LPP study subjects.

1.6 Risks and Benefits

Benefits:

Others with LPP 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 common side effects associated with the use of Deucravacitinib (BMS-986165):

- Very common (occurring in greater than or equal to 10% of subjects), common (occurring in 1-10% of subjects), and rare but serious (occurring in < 1% of subjects) side effects occurring in subjects.

Very Common (affecting more than 10 in every 100 patients) [10,11]
Nasopharyngitis

Common (affecting less than 10 in every 100 patients) [10,11]
Nasopharyngitis, upper respiratory track infection, headache, diarrhea, nausea, arthralgia, cough, hypertension, psoriasis, dyspepsia, myalgia, elevated CPK, rhinitis, sinusitis, back pain, abdominal pain, GERD, herpes simplex infection, canker sores, folliculitis, acne

Rare but Serious [10,11]
Serious allergic reactions, serious infections, certain kinds of cancer including lymphoma, rhabdomyolysis

Hematologic and clinical chemistry lab abnormalities:
Deucravacitinib (BMS-986165) taken systemically can inhibit the growth of blood cells. The risk is low with systemic therapy and subjects will be monitored for any signs of inhibition of their blood counts.

Treatment with Deucravacitinib (BMS-986165) has been associated with dose-related increases in CPK, liver enzymes (AST, ALT). Observed increases have not led serious events or discontinuation of Deucravacitinib (BMS-986165) in prior clinical trial participants. Laboratory abnormalities will be monitored throughout the study.

Infection risk:

There is an increased risk of infection with use of Deucravacitinib (BMS-986165).. The most common serious infections associated with Deucravactinib (BMS-986165) include pneumonia and COVID-19. These will be monitored for. Deucravacitinib (BMS-986165) may increase the risk of infections and reactivation of latent infections such as Tuberculosis, Valley Fever or viral infections such as herpes zoster (shingles) or herpes simplex (cold sore). 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 Deucravacitinib (BMS-986165). Allergic reaction to Deucravactinib (BMS-986165) is a contraindication for continued use.

Venous thromboembolism:
It is unknown whether TYK2 inhibition may be associated with the observed or potential adverse reactions of JAK inhibition. Higher rates of all-cause mortality, including overall thrombosis, deep venous thrombosis, and pulmonary embolism were observed in patients treated with a JAK inhibitor compared to those treated with TNF blockers in rheumatoid arthritis (RA). Deucravacitinib (BMS-986165) is not approved for use in RA. While we do not expect such events to occur, patients should seek medical advice if they experience signs or symptoms of DVT/PE, such as significant shortness of breath, bloody cough, or lower leg swelling, redness, or pain.

Rhabdomyolysis and Elevated CPK
Treatment with Deucravacitinib (BMS-986165) has been associated with an increased incidence of asymptomatic creatine phosphokinase (CPK) elevation and rhabdomyolysis compared to treatment with placebo. Discontinue if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Patients should promptly report any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Cancer Risk:
Deucravacitinib (BMS-986165) may have the potential to affect the subject's immune system; they may be at increased risk for infections. Cancers, including lymphomas, were observed in a few patients in the Deucravacitinib clinical studies; the role of Deucravacitinib in these cancers is uncertain. Long term safety evaluations are ongoing.

Vaccines:
Live vaccines should not be given concurrently with Deucravacitinib (BMS-986165).

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

Lactation Risk:
There are no data on the presence of Deucravacitinib (BMS-986165) in human milk, the effects on the breastfed infant, or the effects on milk production. Deucravacitinib is present in rat milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the risks, women cannot take part in this study if they are 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.

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.

2 Study Objectives

Primary Objective:
To determine the efficacy of Deucravacitinib (BMS-986165) as measured by Lichen Planopilaris Activity Index (LPPAI) score for overall response (Complete and partial responders) at week 24. Percent reduction of baseline LPPAI score after 24 weeks of treatment is defined as follows:

- Complete response: LPPAI reduction greater than 85% from baseline score.
- Partial response: LPPAI reduction between 25-85% from baseline score.
- Non-response: LPPAI reduction of less than 25% from baseline score.

The Lichen Planopilaris Activity Index (LPPAI) is a standardized validated quantitative measure of disease activity [12]. LPPAI score (0-10) is calculated as follows: (pruritus + pain + burning)/3 + (scalp erythema + perifollicular erythema + perifollicular scale)/3 + 2.5 (pull test) + 1.5 (spreading/2). Symptoms and signs are graded on a 4-point scale with 0 = absent, 1 = mild, 2 = moderate, and 3 =severe. Clinical progression and a positive hair pull test are graded 1=yes; 0=no.

Secondary Objective:
To determine the efficacy of Deucravactinib (BMS 986165)) as measured by the changes in PGA of scalp, DQLI score, VAS, VRS, NRS, and Skindex-16.(weeks 0 to 4, weeks 4 to 8, weeks 0 to 8, weeks 8 to 12, weeks 0 to 12, weeks 12 to 16, weeks 0 to 16, weeks 16 to 20, weeks 20 to 24, and weeks 0 to 24).

Exploratory Objectives:
To predict responses and examine the pharmacodynamics of treatment through the identification of unique biomarkers and transcriptomic changes of LPP at week 0 and utilizing single-cell RNA sequencing on responsive and non-responsive tissue at week 4 to correlate these biomarkers with measures of global response:

3 Study Design

3.1 *General Description*

This is a single center, exploratory, open-label, single-arm design study of 22 patients. Adult patients with biopsy proven LPP with active disease will be treated Deucravacitinib (BMS-986165) for 24 weeks. Multiple safety studies have been conducted with Deucravacitinib (BMS-986165) (see Safety) and a dose of 6 mg BID (Cohort A) and dose of 6mg QD (Cohort B) is deemed safe. (Investigator's Brochure)

Individuals over the age of 18 with biopsy proven LPP will be eligible. Individuals must have active disease at baseline. Patients with end-stage scarring hair loss but without significant active disease will be excluded. Prior treatment will be allowed; however, a washout period of 2 weeks for topical and 4 weeks or longer (see Table 1) for systemic agents is required. At the washout period, individuals will undergo evaluation with LPPAI, PGA, DQLI, VAS, VRS, NRS, and Skindex-16. The scalp lesions will be photographed.

Individuals will then initiate treatment with Deucravacitinib (BMS-986165) 6 mg twice daily (Cohort A) and dose of 6mg QD (Cohort B) will be evaluated every 4 weeks and assessed by LPPAI, PGA between weeks 0-24 (see Appendix). Week 24 will be the primary endpoint. Therapy will be stopped and the individuals will be evaluated at week 28 after an observation period of 4 weeks and assessed by the aforementioned assessment tools. Laboratory and safety monitoring will occur at weeks 0, 2, 4, 8, 12, 16, 20, 24, and 28. 3D Photographs will be taken at weeks 0, 2, 4, 8, 12, 16, 20, 24, and 28. Up close photos will be taken of the disease.

A 4 mm punch biopsy of the scalp will be collected for all subjects. Blood collection will include the isolation at week 0, 2, 4, 8, 12, 16, 20, 24, and 28. Blood will be drawn into 5mL vials and subsequently separated. The serum and cell pellet will be stored for future analysis.

Normal patient controls will be obtained from archival tissue collected from normal scalp biopsies at the University of Michigan (Cohort A only). Tissue (up to a 4 mm biopsy sample) will be obtained for analysis from the University of Michigan biobank (Cohort A only).The University of Michigan Biobank has IRB approval for the collection, processing, and storage of samples. All tissue analyses will be conducted at the University of Michigan. Only deidentified data for the control samples will be shared with Mayo Clinic.

Single cell RNA sequencing will be performed at week 0 and week 4 (Cohort A only). A total of up to 30 (14 pre-treatment, 14 post treatment, 4 controls) skin samples will be completed for single cell sequencing (Cohort A only). Bulk RNA sequencing will be completed on up to 30 tissue samples (14 pre-treatment, 14 post treatment, 4 healthy controls) (Cohort A only). Spatial RNA sequencing will be completed on 28 tissue samples (14 pre-treatment, 14 post treatment) (Cohort A only).

Bulk, single-cell and spatial RNA Transcriptome Sequencing: Samples will be prepped and analyzed per bulk, spatial, and single-cell RNA sequencing standard operating procedures of the University of Michigan genomics lab (Cohort A only). Processing and operating protocols are as follows:

Bulk, Single Cell and Spacial RNA Sequencing

Biopsy Processing for bulk and spatial sequencing:
Biopsies will be collected following standard Mayo BAP procedures. Immediately following collection, tissue biopsies will be submerged in formalin. Formalin samples will be shipped to the University of Michigan.

Biopsy Processing for single cell sequencing:

Biopsies will be collected following standard Mayo BAP procedures. Immediately following collection, tissue biopsies will be submerged and frozen in Cryostor CS10 media at a rate of -1°C/minute and stored at -80C. Frozen samples will be shipped within 2 weeks of collection to the University of Michigan. Upon receipt, samples will be stored at -80C until time of processing for single cell sequencing.

Single Cell Sequencing:
Cells will be isolated from cutaneous punch biopsies using collagenase or trypsin containing DNase. Epidermis and dermis are first isolated from one another and then processed separately. Cell quality and quantity will be assessed using Trypan Blue exclusion. Samples with >75% viability will be sequenced without additional cleanup steps. Samples with <75% viability will be further processed to increase concentration of viable cells prior to sequencing.

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.

Primary Outcome measures: The primary outcome measure will be LLPAI score for overall response between week 0 and week 24. Change in LLPAI will also be assessed week 0 to week 2, weeks 0 to 4, weeks 4 to 8, weeks 0 to 8, weeks 8 to 12, weeks 0 to 12, weeks 12 to 16, weeks 0 to 16, weeks 16 to 20,weeks 0 to 20, w change in NRS (week 0 to week 2, weeks 0 to 4, weeks 4 to 8, weeks 0 to 8, weeks 8 to 12, weeks0 to 12, weeks 12 to 16, weeks 0 to 16, weeks 16 to 20, weeks 0 to 20, weeks 0 to 24, week 20 to 24, week 0 to 28, week 24 to 28, weeks 0 to 28), and change in Skindex-16 (week 0 to week 2, weeks 0 to 4, weeks 4 to 8, weeks 0 to 8, weeks 8 to 12, weeks0 to 12, weeks 12 to 16, weeks 0 to 16, weeks 16 to 20, weeks 0 to 20, weeks 0 to 24, week 20 to 24, week 0 to 28, week 24 to 28, weeks 0 to 28).

Exploratory Outcome Measures: To predict responses and examine the pharmacodynamics of treatment through the identification of unique biomarkers and transcriptomic changes of LPP 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: LPPAI, PGA.

3.2 Number of Subjects

22 prospective subjects will be enrolled in this study.

3.3 Duration of Participation

The study consists of 3 epochs: screening/washout period (at least 1 week and up to 4 weeks), treatment epoch (24 weeks from screen/washout), and follow up epoch (4 weeks). The screening and washout period will allow for treatment naïve/ new diagnosis LPP to undergo evaluation and diagnosis and for treatment refractory to undergo a washout. The total duration of the study will be 28 weeks.

Tables:

- **Table-1: Prohibited treatment**

Prohibited treatments[†, ‡]	**Washout period (before Randomization Visit)**
Any concomitant oral or topical JAK inhibitor	Prohibited
Any biologic drug	See below
Immunomodulation treatments for LP[§] [e.g., methotrexate, cyclosporine A, corticosteroids (oral, i.v., intramuscular, s.c., intra-articular, transdermal), mycophenolate mofetil, azathioprine, hydroxychloroquine]	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, finasteride)	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: Washout Periods for Monoclonal Antibodies (Biologic Drugs)

Brand Name	**Generic Name**	**Recommended Minimum Washout (approximately 5 half-lives)**
ACTEMRA	Tocilizumab	8 weeks
CIMZIA	Certolizumab pegol	10 weeks
COSENTYX	Secukinumab	16 weeks
DUPIXENT	Dupilumab	12 weeks
ENBREL	Etanercept	4 weeks
HUMIRA	Adalimumab	8 weeks
KEVZARA	Sarilumab	7 weeks
ORENCIA	Abatacept	8 weeks
REMICADE	Infliximab	6 weeks
RITUXIN	Rituximab	6 months
SIMPONI	Golumimab	10 weeks
STELARA	Ustekinumab	16 weeks
TALTZ	Ixekizumab	10 weeks
TREMFYA	Guselkumab	12 weeks
XOLAIR	Omalizumab	16 weeks

Table-3: Screening and Visits (+/- 3-day window)

	Screening	Day 0	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28
Deucravacitinib (BMS-986165)		X	X	X	X	X	X	X		
Physical Exam	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X	X	X	X
Chest X-ray	X									
Assessments: LPPAI, PGA, Dermatology-Q, VAS, VRS, NRS and Skindex-16		X	X	X	X	X	X	X	X	X
Photographer (hair series)		X	X	X	X	X	X	X	X	X
Punch Biopsy (tissue/serum bank)		X		X						
Serum Pregnancy	X	X		X	X	X	X	X	X	X
Venipuncture	X	X	X	X	X	X	X	X	X	X
Biomarker/RNAseq blood (tissue/serum bank)		X	X	X	x	x	X	x	X	X
CMP	X	x	X	X	X	X	X	X	X	X
Lipid Panel	X	x	X	X	X	X	X	X	X	X
CPK	X	x	X	X	X	X	X	X	X	X
CBC	X	x	X	X	X	X	X	X	X	X
Quantiferon Gold	X									
Hepatitis B	X									
Hepatitis C	X									
HIV	X									
Coccidioidomycosis	X									
Skin swab if needed: (MRSA, fungal culture, Candida, Strep)	X									

3.4 Primary Study Endpoints

Responders (complete and partial responses) by LPPAI score at week 24.

3.5 Secondary Study Endpoints

Change in PGA score (week 24), change in the Dermatology-QLI score (week 24), change in VAS (week 24), change in VRS (week 24), change in NRS (week 24), and change in Skindex-16 (week 24).

3.6 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 and lipid panels that 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.

3.7 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

4 Subject Selection Enrollment and Withdrawal

4.1 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 biopsy proven LPP and active disease

4.2 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 or other adverse reaction to Deucravacitinib (BMS-986165)
- Variants of LPP deemed by the investigators to be inappropriate for Deucravacitinib (BMS-986165)
- 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 inflammatory diseases of the scalp and forms of hair loss other than LPP that might confound the evaluation of the benefit of Deucravacitinib (BMS-986165).
- Tattooing of the scalp that, in the opinion of the investigator, may interfere with accurate assessment of clinical response to Deucravacitinib (BMS-986165).
- 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 immunocompromises the subject and/or places the subject at unacceptable risk for receiving an immunomodulatory therapy
- Moderate-to-severe renal impairment including patients with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2
- Active systemic infections during the 2 weeks prior to randomization (common cold viruses excluded) 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
- Have had any major surgery within 8 weeks prior to screening or will require major surgery during the study that, in the opinion of the investigator would pose an unacceptable risk to the patient.
- Have experienced any of the following within 12 weeks of screening: VTE (DVT/pulmonary embolism [PE]), myocardial infarction (MI), unstable ischemic heart disease, stroke, or New York Heart Association Stage III/IV heart failure.
- Have a history of recurrent (≥ 2) VTE (DVT/PE).
- Have a history of lymphoproliferative disease; have signs or symptoms suggestive of possible lymphoproliferative disease, including lymphadenopathy or splenomegaly; have active primary or recurrent malignant disease; or have been in remission from clinically significant malignancy for <5 years prior to randomization.
- Have had symptomatic herpes zoster infection within 12 weeks prior to randomization.

- Have a history of disseminated/complicated herpes zoster (for example, ophthalmic zoster or CNS involvement).
- ALT or AST >2 x upper limits of normal (ULN); alkaline phosphatase (ALP) ≥2 x ULN; total bilirubin ≥1.5 x ULN; hemoglobin <10 g/dL (100.0 g/L); total white blood cell count <3000 cells/μL (<3.00 x 103/μL or <3.00 billion/L); neutropenia (absolute neutrophil count [ANC] <1500 cells/□L) (<1.50 x 103/□L or <1.50 billion/L); lymphopenia (lymphocyte count <1000 cells/μL) (<1.00 x 103/μL or <1.00 bilion/L); thrombocytopenia (platelets <100,000 cells/μL) (<100 x 103/μL or <100 billion/L)
- Have a positive test for hepatitis B virus (HBV) defined as:
  a. positive for hepatitis B surface antigen (HBsAg), or
  b. positive for hepatitis B core antibody (HBcAb) and positive for hepatitis B virus deoxyribonucleic acid (HBV DNA)

  Note: Patients who are HBcAb-positive and HBV DNA-negative may be enrolled in the study but will require additional HBV DNA monitoring during the study.
- Have hepatitis C virus (HCV) infection (hepatitis C antibody-positive and HCV ribonucleic acid [RNA]-positive).

  Note: Patients who have documented anti-HCV treatment for a past HCV infection AND are HCV RNA-negative may be enrolled in the study.
- Have evidence of HIV infection and/or positive HIV antibodies.
- Have had household contact with a person with active TB and did not receive appropriate and documented prophylaxis for TB.
- Have evidence of active TB or latent TB
- Have evidence of active TB, defined in this study as the following:
  - Positive purified protein derivative (PPD) test (≥5 mm induration between approximately 2 and 3 days after application, regardless of vaccination history), medical history, clinical features, and abnormal chest x-ray at screening.
  - QuantiFERON®-TB Gold test or T-SPOT®.TB test (as available and if compliant with local TB guidelines) may be used instead of the PPD test. Patients are excluded from the study if the test is not negative and there is clinical evidence of active TB.

  Exception: patients with a history of active TB who have documented evidence of appropriate treatment, have no history of re-exposure since their treatment was completed, have no clinical features of active TB, and have a screening chest x-ray with no evidence of active TB may be enrolled if other entry criteria met. Such patients would not be required to undergo the protocol-specific TB testing for PPD, QuantiFERON®-TB Gold test, or T-SPOT®.TB test but must have a chest x-ray at screening (i.e., chest imaging performed within the past 6 months will not be accepted).
- Have evidence of untreated/inadequately or inappropriately treated latent TB, defined in this study as the following:
  - Positive PPD test, no clinical features consistent with active TB, and a chest x-ray with no evidence of active TB at screening; or
  - If the PPD test is positive and the patient has no medical history or chest x-ray findings consistent with active TB, the patient may have a QuantiFERON®-TB Gold test or T-SPOT®.TB test (as available and if compliant with local TB guidelines). If the test results are not negative, the patient will be considered to have latent TB (for purposes of this study); or
  - QuantiFERON®-TB Gold test or T- SPOT®.TB test (as available and if compliant with local TB guidelines) may be used instead of the PPD test. If the test results are positive, the patient will be considered to have latent TB. If the test is not negative, the test may be repeated once within approximately 2 weeks of the initial value. If the repeat test results are again not negative, the patient will be considered to have latent TB (for purposes of this study).
- Have been exposed to a live vaccine within 12 weeks of randomization or are expected to need/receive a live vaccine during the course of the study (with the exception of herpes zoster vaccination).
- Have donated more than a single unit of blood within 4 weeks prior to screening or intend to donate blood during the course of the study.

- Have a history of intravenous drug abuse, other illicit drug abuse, or chronic alcohol abuse within the 2 years prior to screening or are concurrently using, or expected to use during the study, illicit drugs (including marijuana).

4.3 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

4.4 Early Withdrawal of Subjects

4.4.1 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)

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

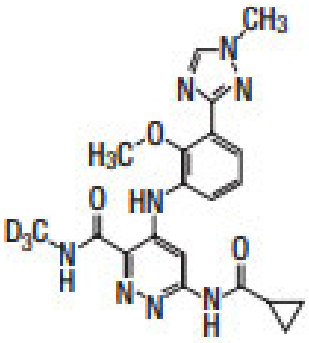
At the time of withdrawal, the reason for withdrawal will be recorded in the CRF. Individuals who withdraw will go into the observation phase for 4 weeks. If a subject withdraws consent, attempts will be made to obtain permissions to collect follow up information.

5 Study Drug

5.1 Description

Deucravacitinib (BMS-986165) is a tyrosine kinase 2 (TYK2) inhibitor and is described chemically as: 6-(cyclopropanecarbonylamido)-4-[2-methoxy-3-(1-methyl-1,2,4-triazol-3-yl)anilino]-N-(trideuteriomethyl)pyridazine-3-carboxamide. The molecular formula is C20H19D3N8O3 and the molecular weight of the free base is 425.47. Deucravacitinib (BMS-986165) has the structural formula: D3C H3C CH3 O O N O N HN N H N N N N H

Deucravacitinib (BMS-986165) **Structural Formula**



Deucravacitinib (BMS-986165) is a white to yellow powder. The solubility of deucravacitinib is pH dependent.

Solubility decreases with increasing pH. Deucravacitinib (BMS-986165) tablets are supplied in 6 mg strength for oral administration. Each tablet contains Deucravacitinib (BMS-986165) as the active ingredient and the following inactive ingredients: anhydrous lactose, croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, and silicon dioxide. In addition, the film coating Opadry® II Pink contains the following inactive ingredients: iron oxide red, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Pharmacodynamics:

In patients with psoriasis, Deucravacitinib (BMS-986165) reduced psoriasis-associated gene expression in psoriatic skin in a dose dependent manner, including reductions in IL-23-pathway and type I IFN pathway regulated genes. Deucravacitinib reduced IL-17A, IL-19 and beta-defensin by 47 to 50%, 72%, and 81 to 84% respectively following 16 weeks of once daily treatment. The relationship between these pharmacodynamic markers and the mechanism(s) by which Deucravacitinib (BMS-986165) exerts its clinical effects is unknown.

Pharmacokinetics:

Following oral administration, Deucravacitinib (BMS-986165) plasma Cmax and AUC increased proportionally over a dose range from 3 mg to 36 mg (0.5 to 6 times the approved recommended dosage) in healthy subjects. The accumulation of Deucravacitinib (BMS-986165) was <1.4-fold following once daily dosing in healthy subjects. The PK of Deucravacitinib (BMS-986165) and its active metabolite, BMT-153261, were comparable between healthy subjects and subjects with psoriasis. The steady state Cmax and AUC24 of deucravacitinib following administration of 6 mg once daily were 45 ng/mL and 473 ng·hr/mL, respectively. The steady state Cmax and AUC24 of the active Deucravacitinib (BMS-986165) metabolite, BMT-153261, following administration of 6 mg once daily were 5 ng/mL and 95 ng·hr/mL, respectively.

Absorption

The absolute oral bioavailability of Deucravacitinib (BMS-986165) was 99% and the median Tmax ranged from 2 to 3 hours in healthy subjects.

Food Effect No clinically significant differences in the pharmacokinetics of Deucravacitinib (BMS-986165) were observed following administration of a high-fat, high-calorie meal (951 kcal in total, with approximate distribution of 52% fat, 33% carbohydrate and 15% protein). Cmax and AUC of deucravacitinib when administered with food were decreased by approximately 24% and 11%, respectively, and Tmax was prolonged by 1 hour. Cmax and AUC of BMT-153261 when administered with food were decreased by approximately 23% and 10%, respectively, and Tmax was prolonged by 2 hours.

Distribution

The volume of distribution of Deucravacitinib (BMS-986165) at steady state is 140 L. Protein binding of Deucravacitinib (BMS-986165) was 82 to 90% and the blood-to-plasma concentration ratio was 1.26.

Elimination
The terminal half-life of Deucravacitinib (BMS-986165) was 10 hours. The renal clearance of Deucravacitinib ranged from 27 to 54 mL/minute.

Metabolism
Deucravacitinib (BMS-986165) is metabolized by cytochrome P-450 (CYP) 1A2 to form major metabolite BMT-153261. Deucravacitinib (BMS-986165) is also metabolized by CYP2B6, CYP2D6, carboxylesterase (CES) 2, and uridine glucuronyl transferase (UGT) 1A9. The active Deucravacitinib metabolite, BMT-153261, has comparable potency to the parent drug, but the circulating exposure of BMT-153261 accounts for approximately 20% of the systemic exposure of the total drug-related components.

Excretion
After a single dose of radiolabeled Deucravacitinib (BMS-986165), approximately 13% and 26% of the dose was recovered as unchanged in urine and feces, respectively. Approximately 6% and 12% of the dose was detected as BMT-153261 in urine and feces, respectively.

Specific Populations
Patients with Renal Impairment
Deucravacitinib (BMS-986165) Cmax was 14% lower and 6% higher in patients with mild (eGFR ≥60 to <90 mL/min/1.73m2) and moderate (eGFR ≥30 to <60 mL/min/1.73m2) renal impairment, compared to subjects with normal renal function (eGFR ≥90 mL/min/1.73m2); no change in Cmax was observed in patients with severe (eGFR <30 mL/min/1.73m2) renal impairment, and ESRD (eGFR <15 mL/min/1.73m2) on dialysis. Deucravacitinib AUCinf was unchanged in patients with mild renal impairment but higher by 39%, 28% and 34% in patients with moderate, severe and ESRD on dialysis, respectively, compared to subjects with normal renal function. BMT-153261 Cmax was 11% lower, 8% lower, 28% higher and 9% higher in patients with mild, moderate, severe renal impairment and ESRD on dialysis, respectively, compared to subjects with normal renal function. BMT-153261 AUCinf was 2% lower, 24% higher, 81% higher and 27% higher in patients with mild, moderate, severe renal impairment and ESRD on dialysis, respectively, compared to subjects with normal renal function. Dialysis did not substantially clear Deucravacitinib (BMS-986165) from systemic circulation (5.4% of dose cleared per dialysis).

Patients with Hepatic Impairment
Deucravacitinib (BMS-986165) Cmax was higher by 4%, 10% and 1% in patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B), and severe (Child-Pugh Class C) hepatic impairment, respectively, compared to subjects with normal hepatic function. Deucravacitinib AUCinf was higher by 10%, 40% and 43% in patients with mild, moderate, and severe hepatic impairment, respectively, compared to subjects with normal hepatic function. BMT-153261 Cmax was lower by 25%, 59% and 79% in patients with mild, moderate, and severe hepatic impairment, respectively, compared to subjects with normal hepatic function. BMT-153261 AUCinf was lower by 3%, 20% and 50% in patients with mild, moderate, and severe hepatic impairment, respectively, compared to subjects with normal hepatic function [see Use in Specific Populations (8.7)].

Body Weight, Gender, Race, and Age
Body weight, gender, race, and age did not have a clinically meaningful effect on Deucravacitinib (BMS-986165) exposure

Potential for Deucravacitinib (BMS-986165)to Affect Other Drugs:

Clinical Trials

No clinically significant differences in the pharmacokinetics of the following drugs were observed when co-administered with Deucravacitinib (BMS-986165): Rosuvastatin, methotrexate, mycophenolate mofetil (MMF) and oral contraceptives (norethindrone acetate and ethinyl estradiol).

In Vitro Studies
Cytochrome P450 (CYP) Enzymes: Deucravacitinib (BMS-986165) is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. Deucravacitinib is not an inducer of CYP1A2, CYP2B6, or CYP3A4.

Carboxylesterase (CES) Enzymes: Deucravacitinib (BMS-986165) is not an inhibitor of CES2.

Uridine diphosphate (UDP)-glucuronosyl transferase (UGT) Enzymes: Deucravacitinib (BMS-986165) is not an inhibitor of UGT1A1, UGT1A4, UGT1A6, UGT1A9, or UGT2B7.

Transporter Systems: Deucravacitinib (BMS-986165) is a substrate of Pgp, BCRP, and OCT1, but not OATP, NTCP, OAT1, OAT3, OCT2, MATE1, or MATE2K. Deucravacitinib (BMS-986165) is an inhibitor of BCRP and OATP1B3, but not an inhibitor of Pgp, OATP1B1, NTCP, BSEP, MRP2, OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2-K.

Potential for Other Drugs to Affect Deucravacitinib (BMS-986165) :

Clinical Trials
No clinically significant differences in the pharmacokinetics of Deucravacitinib (BMS-986165) were observed when co-administered with the following drugs: Cyclosporine (dual Pgp/BCRP inhibitor), fluvoxamine (CYP1A2 inhibitor), ritonavir (CYP1A2 inducer), diflunisal (UGT 1A9 inhibitor), pyrimethamine (OCT1 inhibitor), famotidine (H2 receptor antagonist), or rabeprazole (proton pump inhibitor).

5.2 Treatment Regimen

Subjects will administer Deucravacitinib (BMS-986165) 6 mg tablet twice daily (Cohort A) and 6mg tablet QD (Cohort B) on an empty stomach. Treatment will take place from Day 0 to Week 24.

5.3 Preparation and Administration of Study Drug

The study drug will be supplied by Bristol Myers Squibb to the Mayo Clinic Pharmacy, [redacted], [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 sufficient quantity of tablets at each visit for use between subsequent study visits. Instructions on proper use will be provided to each subject.

5.4 Subject Compliance Monitoring

Compliance will be assessed through direct questioning of subjects.

5.5 Prior and Concomitant Therapy

Individuals on stable doses of medications for chronic illnesses will be allowed. Individuals on immunosuppressive agents for LPP 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 Deucravacitinib (BMS-986165) should use topical broad-spectrum sunscreens with a minimum of SPF30, avoid excess sunlight, and wear sun protective clothing.

5.6 Packaging

The drug will be packaged in bottles with 30 tablets of Deucravacitinib (BMS-986165) 6 mg per bottle. The entire quantity needed for the study will be provided in one shipment. The study drug bottles will be labeled with a diaper label that fully surrounds the bottle. All applicable US FDA required text will be included on the label, included Caution: Limited by U.S. Law to Investigational Use.

5.7 Receiving, Storage, Dispensing and Return

5.7.1 Receipt of Drug Supplies

The drug will be obtained or delivered from Bristol Myers Squibb 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.

5.7.2 Storage

The Deucravacitinib (BMS-986165) drug product should be stored between 20°C and 25°C (68°F and 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F). The supplies will be stored in the Mayo Clinic Pharmacy.

5.7.3 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.

5.7.4 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.

6 Study Procedures

6.1 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
- Lab evaluation of CMP, CBC, Lipid Panel, CPK, TB, and Coccidiomycosis
- We may take swabs to test for certain fungal and bacterial infections
- Complete serum pregnancy if female subject is able to become pregnant

6.2 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 scalp lesions to note any changes
- Take photographs of scalp lesions to document any changes
- Draw blood sample(s)
- Lab evaluation of CMP, CBC, Lipid Panel, and CPK
- Perform skin biopsy (one, 4-6 mm punch biopsy)
- Dispense study drug
- Complete serum pregnancy if female subject is able to become pregnant
- LLPAI
- DLQI
- PGA
- VAS
- VRS
- NRS
- Skindex-16

6.3 Visit 3

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 blood sample(s)
- Lab evaluation of CMP, CBC, Lipid Panel, and CPK
- Dispense study drug
- Adverse events assessment

- LLPAI
- DLQI
- PGA
- VAS
- VRS
- NRS
- Skindex-16

6.4 Visit 4

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
- Lab evaluation of CMP, CBC, Lipid Panel, and CPK
- Perform skin biopsy (one, 4-6 mm punch biopsy)
- Dispense study drug
- Serum pregnancy test if female subject is able to become pregnant
- Adverse event assessment
- LLPAI
- DLQI
- PGA
- VAS
- VRS
- NRS
- Skindex-16

6.5 Visit 5

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
- Lab evaluation of CMP, CBC, Lipid Panel, and CPK
- Dispense study drug
- Complete serum pregnancy if female subject is able to become pregnant
- Adverse events assessment
- LLPAI
- DLQI
- PGA
- VAS
- VRS
- NRS
- Skindex-16

6.6 Visit 6

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
- Lab evaluation of CMP, CBC, Lipid Panel, and CPK
- Dispense study drug
- Complete serum pregnancy if female subject is able to become pregnant
- Adverse events assessment
- LLPAI
- DLQI
- PGA
- VAS
- VRS
- NRS
- Skindex-16

6.7 Visit 7

Week 16 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
- Lab evaluation of CMP, CBC, Lipid Panel, and CPK
- Dispense study drug
- Complete serum pregnancy if female subject is able to become pregnant
- Adverse events assessment
- LLPAI
- DLQI
- PGA
- VAS
- VRS
- NRS
- Skindex-16

6.8 Visit 8

Week 20 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
- Lab evaluation of CMP, CBC, Lipid Panel, and CPK
- Dispense study drug
- Complete serum pregnancy if female subject is able to become pregnant
- Adverse events assessment
- LLPAI
- DLQI
- PGA
- VAS
- VRS
- NRS
- Skindex-16

6.9 Visit 9

Week 24 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
- Lab evaluation of CMP, CBC, Lipid Panel, and CPK
- Complete serum pregnancy if female subject is able to become pregnant
- Adverse events assessment
- LLPAI
- DLQI
- PGA
- VAS
- VRS
- NRS
- Skindex-16

6.10 Visit 10

Week 28 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
- Lab evaluation of CMP, CBC, Lipid Panel, and CPK
- Complete serum pregnancy if female subject is able to become pregnant
- Adverse events assessment

- LLPAI
- DLQI
- PGA
- VAS
- VRS
- NRS
- Skindex-16

7 Statistical Plan

7.1 Sample Size Determination

Data analysis: Due to the costs associated with a study, we propose a single armed study of 22 LPP subjects, for a total of 22 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.

7.2 Statistical Methods

Descriptive Statistics

Sample Size Computation and Power Analysis:
The sample size for this pilot study is set at 22 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 22 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 McNemar's or Bowker's tests will be used to quantify changes in categorical variables. Complete response rate and complete/partial response rate and their corresponding 95% confidence intervals will be calculated and estimated using exact binomial method. Spaghetti plots will be used to visualize trend of the LPPAI score, PGA score, and Dermatology-QLI score at each time points for each individual..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:
Bulk, Spatial, and Single-cell RNA Seq analysis: will be performed according to standard operating procedures of Mayo Clinic and University of Michigan genomics lab and bioinformatics. We will perform bulk, single cell and spatial sequencing pre and post therapeutically on tissue. Using these genomic techniques, we can determine differences within samples as well as between diseases in as few as 1-3 samples. Larger sample sizes will allow for confirmation of findings.

We will use bulk RNA sequencing to identify the enriched pathways of LPP and the pathway changes associated with treatment response. We will also define the single cell composition of LPP. We will examine the changes

pre and post therapeutic in each cell population in the tissue. We will identify the pathogenic T-cell as well as fibroblast based upon pre- and post- therapeutic changes of sub-populations of each cell type that correlate with response. Finally, we will map the pathogenic cells in space by integrating the single cell and spatial RNA sequencing data. This will allow us to determine a possible mechanism of action of both the T-cell inflammation and Fibroblast stimulation in LPP. Finally, we will validate our single cell and spatial findings using bulk RNA sequencing and immunohistochemical staining.

7.3 Subject Population(s) for Analysis

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

8 Safety and Adverse Events

8.1 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.

Temporary Interruption of Investigational Product: In some circumstances, patients may need to temporarily interrupt treatment as a result of AEs or abnormal laboratory values that may have an unclear relationship to investigational product. For the abnormal laboratory findings and clinical events (regardless of relatedness), specific guidance is provided for temporarily interrupting treatment and when treatment may be restarted. Retest frequency and timing of follow up laboratory tests to monitor the abnormal finding is at the discretion of the investigator. Investigational product that was temporarily interrupted because of an AE or abnormal laboratory value may be restarted at the discretion of the investigator.

- Absolute Neutrophil Count (ANC): Treatment should be interrupted if ANC < 1 x 109 cells/L and may be restarted once ANC return above this value
- Absolute Lymphocyte Count (ALC): Treatment should be interrupted if ALC < 0.5 x 109 cells/L and may be restarted once ALC return above this value
- Hemoglobin (Hb): Treatment should be interrupted if Hb < 8 g/dL and may be restarted once Hb return above this value
- Hepatic transaminases: Treatment should be temporarily interrupted if drug-induced liver injury is suspected

Permanent Discontinuation from Investigational Product: Investigational product must be permanently discontinued if the patient or the patient's designee requests to discontinue investigational product. Discontinuation of the investigational product for abnormal liver tests should be considered by the investigator when a patient meets 1 of the following conditions:

- ALT or AST >8 x ULN
- ALT or AST >5 x ULN for more than 2 weeks after temporary interruption of investigational product
- ALT or AST >3 x ULN and total bilirubin level (TBL) >2 x ULN or international normalized ratio (INR) >1.5
- ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

- ALP >3 x ULN that is deemed to be of liver origin and drug-related
- ALP >2.5 x ULN and TBL >2 x ULN
- ALP >2.5 x ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- Investigational product should be permanently discontinued if any of the following laboratory abnormalities are observed:
- White blood cell count <1000 cells/□L (1.00 x 103/□L or 1.00 billion/L)
- ANC <500 cells/□L (0.50 x 103/□L or 0.50 billion/L)
- Lymphocyte count <200 cells/□L (0.20 x 103/□L or 0.20 billion/L)
- Hemoglobin <6.5 g/dL (<65.0 g/L)

Hepatitis B virus DNA testing will be performed in enrolled patients who tested positive for HBcAb at screening. Patients who are HBcAb-positive and HBV DNA-negative (undetectable) at Visit 1 will require HBV DNA monitoring every 3 months and at the patient's last visit, regardless of their hepatitis B surface antibody (HBsAb) status. The following actions should be taken in response to HBV DNA test results:

- If a single result is obtained with a value "below limit of quantitation," the test should be repeated within approximately 2 weeks.
- If the repeat test result is "target not detected," monitoring may resume according to the study schedule.
- If the patient has 2 or more test results with a value "below limit of quantitation" during the study, HBV DNA testing should be performed approximately once per month for the remainder of the study and referral to a hepatologist is recommended.
- If a result is obtained with a value above limit of quantitation at any time during the study, the patient will be permanently discontinued from investigational product and should be referred to a hepatology specialist immediately

Supplemental 1: Appropriateness of Measures

Skin Scoring:
LPPAI
Disease activity in LPP can be measured with the well validated Lichen Planopilaris Activity Index, first developed in 2010. LLPAI quantifies LPP activity using the following variables: itch, pain, burn, scalp erythema, perifollicular erythema, perifollicular scaling, pull test, and spreading.

PGA
The use of PGA is well validated in other inflammatory skin conditions and is frequently used as a primary or secondary endpoint assessment tool. The assessment measures the overall response to treatment as assessed by the physician.

Itch Scoring:

The VAS, VRS, NRS and Skindex-16 are all well validated measure of itch. The VAS, VRS and NRS scores focus on a gestalt of itch. The Skindex-16 scoring system focuses on 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. Any woman with a confirmed positive pregnancy test during screening is not eligible for the study. A positive u 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:
Blood pressure and heart rate will be monitored at all patient visits. Blood pressure will be measured by standard procedure with sphygmomanometer with patient in seated position and arm on the table at chest height. Heart rate will be measured with pulse oximeter.

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 Florida. 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.

8.2 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.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriate 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.

Relationship of adverse events to study drug

For all AEs, the investigator will assess the causal relationship between the study drug and the AE using his/her clinical expertise and judgment according to the following algorithm that best fits the circumstances of the AE. The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment or pathologies. A "reasonable possibility" means that there is a cause and effect relationship between the investigational product, study device and/or study procedure and the AE. The investigator answers yes/no when making this assessment.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

8.3.1 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 Bristol Myers Squibb and Company SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours \ 1 Business Day of becoming aware of the event. SAEs must be recorded on either CIOMS, MedWatch, or approved study specifi/institutional SAE form. Any SAEs experienced after the 30-days period should only be reported to Bristol Myers Squibb and Company 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.

BMS Reporting:
SAE Email Address: [redacted]
SAE Facsimile Number: [redacted]

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours \ 1 Business Day to BMS using the same procedure used for transmitting the initial SAE report.
All SAEs should be followed to resolution or stabilization.

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 5.0 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).

8.3.2 Sponsor-Investigator reporting: Notifying the FDA

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

All Serious Adverse Events ("SAE") required to be reported pursuant to the Protocol shall be provided to Bristol Myers Squibb and Company 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 Bristol Myers Squibb and Company's contact below. SAE Reports will be sent to the email address provided below. By sending to this e-mail address, the Bristol Myers Squibb and Company Pharmacovigilance group and the Bristol Myers Squibb and Company 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 Bristol Myers Squibb and Company for sponsored trials.

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant).
The Sponsor-Investigator must immediately notify [redacted] of this event and complete one of the following forms within 24 hours of awareness of the event via either the CIOMS, MedWatch or appropriate Pregnancy Surveillance Form in accordance with SAE reporting procedures.
Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.
Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the CIOMS, MedWatch, BMS Pregnancy

Surveillance Form, or approved site SAE form. A BMS Pregnancy Surveillance Form may be provided upon request.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for Sponsor-Investigator or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

ADVERSE EVENT RECONCILIATION PROCESS

The Sponsor-Investigator (or designee) will reconcile the clinical database AE cases (case level only) transmitted to BMS Global Pharmacovigilance [redacted].

- The Sponsor-Investigator will request the SAE reconciliation report (and include the BMS protocol number) from BMS GPV&E [redacted]) every 3 months and prior to data base lock or final data summary
- GPV&E will send the Sponsor-Investigator the report to verify and confirm all AE and SAEs have been transmitted to BMS GPV&E.
- The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Sponsor-Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS [redacted]

Bristol Myers Squibb and Company contact for e-mail transmission of individual SAE reports.:

Safety Contacts:

Thomas Scharnitz, MD

[redacted]

Procedure for Reporting of Pregnancy and Lactation to the Sponsor (Bristol Myers Squibb**)**

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.

8.4 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.

8.5 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.

9 Data Handling and Record Keeping

9.1 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 Section*).* 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.

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.

9.2 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.

9.3 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

9.4 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 [redacted]

Whichever is longer

10 Study Monitoring, Auditing, and Inspecting

10.1 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.

10.2 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.

11 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.

12 Study Finances

12.1 Funding Source

Bristol Myers Squibb and Company is funding this research study.

12.2 Subject Stipends or Payments

None

13 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.

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15 Attachments

Appendix:

Physician Global Assessment: [12,13]
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

Lichen Planopilaris Activity Index
LPPAI score (0–10) is calculated as follows: (pruritus + pain + burning)/3+ (scalp erythema + perifollicular erythema + perifollicular scale)/3 + 2.5 (pull test) +1.5 (spreading/2).

LPPAI	**0 (Absent)**	**1 (Mild)**	**2 (Moderate)**	**3 (Severe)**
Symptoms				
Pruritis				
Pain				
Burning				
Signs				
Erythema				
Perifollicular erythema				
Perifollicular keratosis				

Pull Test	**0 (negative)**	**1 (positive)**

Spreading of Disease	**0 (no spreading)**	**1 (indeterminate)**	**spreading**

Itch-
Numerical Rating Scale (NRS) (bottom)- [14,15]

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

Pruritus Verbal Rating Scale (VRS)

On average, please rate your itch over the past 24 hours:

□ 0 (None)
□ 1 (Mild)
□ 2 (Moderate)
□ 3 (Severe)

At its worst, please rate your itch in the last 24 hours:

□ 0 (None)
□ 1 (Mild)
□ 2 (Moderate)
□ 3 (Severe)

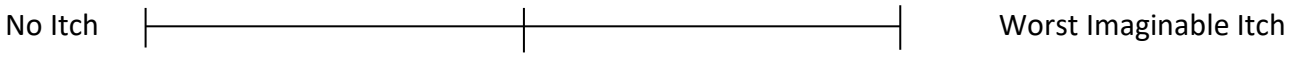
Pruritus Visual Analogue Scale

Please rate your **average** itch level over the past day by placing a vertical mark on the line below.

No Itch ——————————————— Worst Imaginable Itch

_____._____cm

Please rate your **worst** itch level over the past day by placing a vertical mark on the line below.



_____._____cm

VAS score interpretation:

VAS 0 = No itch
VAS <3 = Mild itch
VAS ≥3 <7 = Moderate itch
VAS ≥7 <9 = Severe itch
VAS ≥9 = Very severe itch

Skindex-16-

Skindex 16 [16,17]-

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

16 Dermatology Life Quality Index (DLQI)

MRN: ……

Date: ……

Score: ……

Name: ……

17 This questionnaire aims to measure how much your LLP has affected your life over the LAST MONTH. Please check one box for each question.

1. Over the last week, how itchy, sore, painful or stinging has your skin been?

Very much ☐ A lot ☐ A little ☐ Not at all ☐

2. Over the last week, how embarrassed or self conscious have you been because of your rash?

Very much ☐ A lot ☐ A little ☐ Not at all ☐

3. Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?

Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant ☐

Over the last week, how much has your skin influenced the clothes you wear? Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant ☐

4. Over the last week, how much has your skin affected any social or leasiure activity?

Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant ☐

5. Over the last week, how much has your skin made it difficult for you to do any sport? Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant ☐

6. Over the last week, has your skin prevent you from working or studying? Yes ☐ No ☐ If "No" over the last week how much has your skin been a problem at work or studying?

A lot ☐ A little ☐ Not at all ☐

7. Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?

Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant ☐

8. Over the last week, how much has your skin caused any sexual difficulties?

Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant ☐

9. Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?

Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant ☐

Very much ☐ A lot ☐ A little ☐ Not at all ☐

A little ☐ Not at al