Washington University in St. Louis
SCHOOL OF MEDICINE

Brian S Kim, MD, MTR, FAAD
Associate Professor of Medicine
Co-Director, Center for the Study of Itch and Sensory Disorders
Department of Medicine
Division of Dermatology
St. Louis, MO 63110

16 March 2020

To Whom it May Concern:

Please find enclosed the protocol and informed consent form for the proof-of-concept open-label clinical trial entitled listed as “A Study Examining the Medication Apremilast as Treatment for Chronic Itch” on ClinicalTrials.gov (NCT03239106).

Please see attached/uploaded documents.

Please do not hesitate to contact me directly should anyone have questions at (314) 273-1376.

Sincerely,

Brian S. Kim, MD, MTR, FAAD
Associate Professor of Medicine (Dermatology), Anesthesiology, and Pathology and Immunology
Co-Director, Center for the Study of Itch and Sensory Disorders
Department of Medicine/Division of Dermatology
Washington University School of Medicine

Clinical Study Protocol

APREMILAST (CC-10004)

An Open-Label Pilot Study of Apremilast in Chronic Idiopathic Pruritus

Product:	**Apremilast**
IND Number:	**Exempt**
EudraCT Number:	
Phase of Study:	**2**
Sponsor:	**Washington University School of Medicine** **Division of Dermatology** **Campus Box 8123** **660 S. Euclid Ave** **St. Louis, MO 63110**
Date of Protocol:	**29 November 2017**

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

SYNOPSIS

Name of Investigational Product: Arepmilast CC-10004	
Title of Study: An Open-Label Pilot Study of Apremilast in Chronic Idiopathic Pruritus	
Protocol Number:	**Study Phase:** 2
Indication: Chronic Idiopathic Pruritus	

Primary Objectives:

- To demonstrate that apremilast 30 mg taken twice daily (BID) results in improvement in Numerical Rating Scale (NRS) itch score from Baseline.

Secondary Objective:

Key Secondary objectives:

- To demonstrate that apremilast 30 mg taken twice daily (BID) results in improvement in Dermatology Life Quality Index (DLQI) from Baseline.

Exploratory Objectives:

- To identify whether skin transcriptomic signatures are altered in response to treatment with apremilast by RNA-seq analysis.

Primary Endpoints:

- Absolute change from Baseline in Numerical Rating Scale (NRS) itch score to week 16. The NRS itch score will be recalled from the prior 24 hours first and then the prior 1 week.

Secondary Endpoints:

Key secondary endpoints:

- Absolute change from Baseline in Dermatology Life Quality Index (DLQI) to week 16.

Other secondary endpoints:

- NRS itch score at Screening, Baseline, Weeks 2, 4, 8, 12 and 16, and 18.
- Dermatology Life Quality Index (DLQI) at Screening, Baseline, Weeks 2, 4, 8, 12, 16, and 18.
- AEs; performing physical examinations; collecting vital signs; and collecting laboratory data for hematology and serum chemistry.

Exploratory Endpoints:

- Skin RNA-seq analysis at Week 0 and Week 16.

Overall Study Design:

This study is an open label pilot study to test the efficacy of apremilast in the treatment of chronic idiopathic pruritus (CIP). Ten subjects who meet the eligibility criteria will be enrolled. The total duration of subject participation will be seven study visits over approximately 22 weeks. All subjects will receive apremilast 30 mg by mouth BID for 16 weeks. Subjects will have follow-up assessments 2 weeks after the last dose.

Study Population: Men or women, aged ≥ 18 years, who have been diagnosed with CIP with a NRS itch score of ≥ 7.

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

- Male and non-pregnant, non-lactating female subjects aged 18 years or older
- Diagnosed with chronic idiopathic pruritus (CIP) with an NRS Itch Score of ≥ 7 at both Screening and Baseline
- Diagnosis of CIP for at least 6 weeks prior to screening
- Willingness to avoid pregnancy or fathering of children
- Ability and willingness to provide written informed consent
- Willing and able to comply with all study requirements and restrictions
- Willing to not participate in any other interventional trial for the duration of their participation
- Subjects must be in good health as determined by medical history, physical examination, electrocardiogram, clinical laboratory tests and vital signs
- Failure of a course 2-week course of treatment with topical triamcinolone 0.1% ointment BID
- Histopathological demonstration of skin eosinophils, mast cell activation, lymphocytic infiltration, and/or dermal edema

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

- Chronic pruritus due to a defined primary dermatologic disorder (e.g., atopic dermatitis, psoriasis, etc.)
- Patients with a prior diagnosis of excoriation disorder
- Use of topical treatments for CIP (other than bland emollients) within 1 week of Baseline
- Systemic immunosuppressive or immunomodulating drugs within 4 weeks of Baseline
- Subjects with cytopenias at screening, defined as:
  - Leukocytes < 3×10^9/L.
  - Neutrophils < lower limit of normal.
  - Lymphocytes < 0.5×10^9/L
  - Hemoglobin < 10 g/dL.
  - Platelets < 100×10^9/L.
- Unwilling or unable to follow medication restrictions described in **Section 5.6.3**, or unwilling or unable to sufficiently washout from use of restricted medication
- Under medical treatment for a skin disease with a therapy listed in the prohibited medications section that may influence the results of the study
- Current clinically significant cardiovascular, respiratory, neurologic, hepatic, hematopoietic, renal gastrointestinal, endocrine or metabolic dysfunction unless currently controlled and stable, including (but not limited to) the following:

  Positive for hepatitis C antibody test (anti-HCF)

Positive for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb) Positive for HIV (DUO test, p24 antigen) • Active malignancy • Active substance abuse or history of substance abuse within 6 months of screening • History (including family history) or current evidence of congenital long QT syndrome or known acquired QT prolongation • Exposure to any investigational medication, including placebo, within 60 days of the Baseline Visit • Subjects who had previously received apremilast • Subjects with severely impaired liver function (Child-Pugh Class C) or end-stage renal disease on dialysis or at least 1 of the following: – Serum creatinine > 1.5 mg/dL – Alanine aminotransferase or aspartate aminotransferase ≥ 1.5 × upper limit of normal • Anyone affiliated with the site or sponsor and/or anyone who may consent under duress • Any other sound medical reason as determined by the Investigator including any condition which may lead to an unfavorable risk-benefit of study participation, may interfere with study compliance or may confound study results
Apremilast tablet/Study Drug, Dosage, and Mode of Administration: Study drug will be supplied as apremilast 10 mg tablets and given orally in the following manner. Initial: 10 mg in the morning. Titrate upward by additional 10 mg per day on days 2 to 5 as follows: Day 2: 10 mg twice daily; Day 3: 10 mg in the morning and 20 mg in the evening; Day 4: 20 mg twice daily; Day 5: 20 mg in the morning and 30 mg in the evening. Maintenance dose: 30 mg twice daily starting on day 6.
Reference Therapy, Dosage, and Mode of Administration: As currently prescribed and indicated for psoriatic arthritis and plaque psoriasis.
Study Schedule/Procedures: All subjects will have visits at Screening, Baseline, and Weeks 2, 4, 8, 12, 16 and 18. Adverse events (AEs), medication history, clinical assessments, physical exam, and vital signs will be performed at each visit. Clinical safety laboratories will be performed at screening and Week 16 (EOT). All laboratory assessments will be performed using the local Barnes-Jewish Hospital laboratory except for urine pregnancy tests (as applicable). NRS and DLQI scoring will be performed by a research nurse. Two skin biopsies will be performed at the most pruritic site at Baseline and at Week 16 (adjacent to the initial biopsy site) for histopathological analysis and RNA-seq transcriptional analysis. After the end-of-treatment visit (Week 16, or early termination), subjects will have follow-up assessments 2 weeks later to monitor for durability of effect (relapse rate), AE, medication
Estimated Duration of Participation: The screening period is up to 4 weeks. The treatment period is 16 weeks with active treatment. Follow-up is 2 weeks following last treatment dose. Total duration is up to 22 weeks.
Estimated Number of Subjects: Approximately 10 subjects.
Principal Coordinating Investigator: Kim, Brian S., MD/MTR, Washington University School of Medicine, St. Louis, MO, USA
Statistical Methods: Given that the same subject will be compared at two time points, a

paired t-test analysis of the NRS itch score will be performed. However, additional visits in between the two time points will provide additional data points that can be further incorporated for more extensive statistical analyses. As all subjects will start at a high NRS score (≥ 7), there will be very little variability in the initial study population. Based on a random sampling of 10 patients with CIP in our clinic, we identified a mean NRS score of 8.8 with a standard deviation of 1.1. The NRS scale runs from 0 to 10. Therefore any significant decrease in our NRS score will be captured with even a small sample size. Thus, N = 10 should be more than sufficient based on this amount of variance and starting NRS score.

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LIST OF ABBREVIATIONS

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

Term	Explanation
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
APR	Apremilast
AST	Aspartate Aminotransferase
BID	Twice Daily
cAMP	Cyclic Adenosine Monophosphate
CFR	Code of Federal Regulations
CIP	Chronic Idiopathic Pruritus
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
EOS	End of Study
EOT	End of Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GvHD	Graft-versus-Host Disease
HCV-RNA	Hepatitis C Virus Ribonucleic Acid
HIPAA	Health Insurance Portability and Accountability Act of 1996
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN-γ	Interferon-γ
IL	Interleukin
IN	Investigator Notification
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
LPS	Lipopolysaccharide

Term	Explanation
MCP-1	Monocyte Chemotactic Protein-1
MedDRA	Medical Dictionary for Regulatory Activities
NK	Natural Killer
NOAEL	No-Observed-Adverse-Effect Level
OAT	Organic Anion Transporter
OATP	Organic Anion Transporter Polypeptide
PASI	Psoriasis Area Severity Index
PDE	Phosphodiasterase
PK	Pharmacokinetic
PsA	Psoriatic Arthiritis
QD	Once Daily
RA	Rheumathoid Arthritis
Relapse	Increased findings of itch on history, physical examination, NRS itch score, and DLQI score following a defined clinical response
RNA-seq	RNA sequencing
SAE	Serious Adverse Event
sPGA	Static Physcian Global Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TNF	Tumor Necrosis Factor
ULN	Upper Limit of Normal

1. INTRODUCTION

Apremilast (APR, CC-10004) is an oral small-molecule inhibitor of the enzyme phosphodiesterase 4 (PDE4) that operates intracellularly to modulate a network of pro- and anti-inflammatory processes. PDE4 is a cyclic adensosine monophosphate(cAMP)-specific PDE that is present in inflammatory cells. By inhibiting PDE4, apremilast reduces the inflammatory response implicated in diseases such as psoriasis and psoriatic arthritis (PsA). Elevating intracellular cAMP downregulates inflammatory response by modulating expression of TNF-a, IL-23, IL-17 and other inflammatory cytokines. Apremilast has demonstrated broad anti-inflammatory effects in vitro, namely the inhibition of the production of multiple mediators including TNF-α, IFN-γ, CXCL9 (monokine induced by IFN-γ, or MIG), CXCL10 (IFN-γ-induced protein of 10 kDa, or IP-10), IL-2, IL-12, IL-23, macrophage inflammatory protein (MIP)-1α, monocyte chemoattractant protein (MCP)-1 and granulocyte macrophage-colony stimulating factor (GM-CSF) from PBMCs (**Schafer et al. 2010, Schafer et al. 2013**).

Apremilast is approved in 36 countries worldwide for the treatment of psoriasis and psoriatic arthritis (PsA). Apremilast is under clinical development for the treatment of various immune-mediated inflammatory disorders, such as psoriasis, psoriatic arthritis (PsA), rheumatoid arthritis (RA), Behçet's disease, ankylosing spondylitis (AS), atopic dermatitis (AD), and ulcerative colitis (UC).

1.1. Chronic Idiopathic Pruritus (CIP)

Chronic pruritus affects approximately 25% of the elderly population and its incidence is increasing throughout the world (**Valdes-Rodriguez 2015**). A variety of conditions manifest as chronic pruritus including AD, psoriasis and cutaneous T cell lymphoma (CTCL). However, it is believed that a significant proportion of the population suffers from pruritus of unknown origin (PUO) or chronic idiopathic pruritus (CIP). We have recently identified that these patients have severe, chronic pruritus in the absence of other known causes of pruritus such as primary inflammatory skin diseases, dialysis-dependent renal failure, biliary disease, or malignancy. However, despite the absence of a primary dermatologic process, we have identified that many of these patients demonstrate low-grade skin inflammation as determined by histopathological analysis consisting of either dermal edema, eosinphilic infiltration, mast cell activation and/or lymphocytic inflammation (**Xu et al. 2016**).

1.2. Inflammation and CIP

Mild type 2 inflammation is widely believed to underlie the pathogenesis of CIP. Indeed, in new studies, we have identified that patients with CIP exhibit peripheral blood and skin eosinophilia consistent with a type 2 immune profile (**Xu et al. 2016**). In new studies, we have identified that many cytokine receptors including, but not limited to, receptors for type 2 cytokines are present on itch-sensory neurons. Thus, we hypothesize that the anti-inflammatory effects of PDE4 inhibition may extend beyond immune cells to neurons. Indeed, PDE4 is known to be expressed in sensory neurons.

1.3. Role of Phosphodiasterase in CIP

Apremilast is an oral PDE4 inhibitor that has been shown to regulate inflammatory mediators. PDE4, the dominant phosphodiesterase expressed in immune cells, degrades cyclic AMP (cAMP) into AMP. Phosphodiesterase 4 inhibition thereby elevates intracellular cAMP, which can down-regulate the inflammatory responses through mechanisms such as partially inhibiting expression of inflammatory cytokines and increasing expression of anti-inflammatory mediators such as IL-10. However, PDE4 is also known to be expressed in sensory neurons. Further, in preliminary work, we have identified that many cytokine receptors traditionally ascribed to immune cells are functional on sensory neurons. Taken together, the central hypothesis of this study is that apremilast may function as an anti-itch neuromodulatory agent through dual functions: 1) inhibition of PDE4 in immune cells and 2) inhibition of itch-sensory neuronal responses. The dual mechanism(s) of action may serve as an ideal agent for the treatment of CIP which is associated with both immune dsyregulation and neuronal dysfunction.

1.4. Apremilast Pharmacology and Pharmacokinetics

Apremilast is an orally active compound that modulates multiple inflammatory pathways through PDE4 inhibition. Specifically, apremilast blocks the degradation of cAMP via potent inhibition of the PDE4 enzyme, resulting in an increase of cAMP in PDE4-expressing cells including monocytes, T-cells, and neutrophils. The pharmocodynamic properties of apremilast include modulation of human PBMC- and T-cell-derived cytokines and anti-inflammatory, anti-nociceptive and anti-angiogenic effects. Apremilast elevates IL-10 production and inhibits gene expression of TNFa, IFN-γ, IL-12 and IL-23. Additionally, PDE4 is also expressed in sensory neurons provoking the hypothesis that it may also inhibit the effects of various pro-inflammatory mediators at the sensory neuronal level.

Apremilast is highly selective for PDE4. The results of studies evaluating the specificity of apremilast for PDE4 inhibition indicated that apremilast was approximately 279- to 40,000-fold more selective for PDE4 enzyme inhibition compared with the other PDE enzymes and showed no inhibition or binding to other receptors, kinases, or enzymes. Results from various in vitro cellular assays demonstrated that apremilast inhibits production of various cytokines and chemokines, such as TNF-α, IL-2, IL-5, IL-12, IL-13, IL-17, IL-23, IFN-α, IFN-γ, IFN-γ inducible protein-10 (IP-10), granulocyte macrophage colony-stimulating factor (GM-CSF), macrophage inflammatory protein-1 alpha (MIP-1α), monocyte chemotacticprotein-1 (MCP-1), and monokine induced by IFN-γ (MIG), by keratinocytes, monocytes, neutrophils, plasmacytoid dendritic cells (pDCs), and T-cells. Also, apremilast elevates IL-10 production in PBMCs.

Oral apremilast is absorbed with peak plasma concentrations occurring at a median time of approximately 2.5 hours. Co-administration with food does not alter the extent of absorbtion. Human plasma protein binding of apremilast is approximately 68% with mean apparent volume of distribution of 87 L.

Additional details as to the pharmacology and pharmacokinetics of apremilast may be found in the Investigator's Brochure (**see attached**).

1.5. Apremilast Relevant Non-Clinical Data

In animal models of acute gastrointestinal (GI), rheumatologic, and dermatologic inflammation, apremilast has demonstrated anti-inflammatory activity, including inhibition of systemic TNF-α production and neutrophil infiltration, and was shown to inhibit arthritogenic edema in a manner similar to etanercept (TNF-α receptor Ig fusion protein).

Apremilast has been tested in animal models of acute GI, rheumatologic, abd dermatologic inflammation. In an acute inflammation model, PO administration was found to lower mouse serum TNF-α levels in response to systemic lipospolysaccharide (LPS) endotoxin indicating possible anti-inflammatory effects. Apremilast significantly decreased rat paw edema and demonstrated biologically relevant increases in both mechanical and thermal pain thresholds. In the combined mAb/LPS-induced arthritis model, apremilast significantly inhibited arthritic activity (notable hind paw swelling) in a manner similar to oral administration of dexamethasone and intraperitoneal entanercept. In two models of contact dermatitis, APR was shown to inhibit ear thickness and swelling and MCP-1 protein levels were decreased at the site of inflammation. Using the Irwin screen, mouse central nervous system changes were dose related and limited in duration. At 500 mg/kg, no behavioral or physiological changes were noted compared to the vehicle. At 1000 mg/kg, slight lacrimation and ptosis were noted appearing at sixty minutes and disappearing at three hundred minutes. Cardiovascular effects when tested in dogs at dose of 5 mg/kg assessed pulse pressure, cardiac contractility, R-R and QT intervals and no parameters were considered adverse. Higher doses elicted moderate increase in heart rate and dP/t max, reduction in R-R and QT interval however QTc was unchanged at all doses. Except for a small increase in peak flow following high doses (5 mg/kg), no changes in respiratory depth or rate at any dose level was observed.

In vitro studies suggest that apremilast is not likely to cause drug-drug interactions due to inhibition or induction of the metabolism of co-administered CYP substrates. Since the clearance of apremilast occurs via multiple routes, namely oxidative and non-CYP-mediated hydrolytic metabolism, it is unlikely that co-administered CYP inhibitors will decrease its clearance to a clinically relevant extent. Likewise, it is unlikely that coadministration of inhibitors or substrates of drug transporters P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporter (OAT) 1, OAT3, organic cation transporter (OCT) 2, organic anion transporting polypeptide (OATP) 1B1, or OATP1B3 will lead to pharmacokinetic drug-drug interactions with apremilast.

Pharmacokinetic parameters of apremilast following PO and IV administration to mice, rats, gravid rabbits and monkeys (PO only) have been assessed. In animals, systemic clearance of apremilast (or apparent clearance after PO administration) varied widely, with mice and female rats exhibiting low clearance, and male rats and female rabbits exhibiting high clearance. In monkeys, the apparent clearance after PO administration was moderate. The volume of distribution (Vd) was moderate and approximately 2- to 3-

fold body water volume, suggesting blood tissue distribution of this compound. The terminal half-lives of apremilast in animals were short and ranged from 1 to 3 hours. The oral absorption of apremilast was high in mice and monkeys (≥ 70%). The oral bioavailability of apremilast was moderate (mouse and rat) to negligible (rabbit), suggesting that it is subject to first-pass extraction to varying degrees in animals. Notable gender differences were observed in rats, but not in mice and monkeys. When administered PO over a wide dose range, the exposure of apremilast increased in a less than dose-proportional manner, suggesting that apremilast absorption is solubility limited. On multiple dosing, a consistent trend of either decreasing or increasing exposures was not observed in mice and monkeys. The asymmetric center of apremilast was resistant to inversion in all the 4 animal models used for toxicity assessments. Apremilast was evaluated for photoxicity and showed no phototoxic or cytotoxic effect.

Additional details as to the pharmacology of apremilast may be found in the Investigator's Brochure (**see attached**).

1.6. Clinical Experience

As of 30 Nov 2015, apremilast had been administered at daily doses ranging from 10 to100 mg/day to over 5500 subjects in Celgene-sponsored studies, including over 4800 subjects who received apremilast in Phase 2 or Phase 3 studies in psoriasis, PsA, AS, ulcerative colitis (UC), AD, Behcet's disease (BD), or RA.

To date, 28 clinical studies have been completed, including 20 Phase 1 studies and 8 Phase 2 studies. A total of 15 clinical studies are currently ongoing: 4 Phase 2 studies (2 in subjects with psoriasis [including 1 pediatric study], 1 in subjects with AD, and 1 in subjects with UC), 10 Phase 3 studies (5 insubjects with PsA, 3 in subjects with psoriasis, 1 in subjects with BD, and 1 in subjects with AS), and 1 Phase 4 study (in subjects with psoriasis). A summary of all completed and ongoing Celgene-sponsored clinical studies with apremilast as of 30 Nov 2015 is presented. In addition, there have been 10 investigator-initiated trials (IITs) completed in subjects with AD, contact dermatitis, AS, cutaneous lupus, cutaneous sarcoidosis, lichen planus, osteoarthritis, prostatitis, vulvodynia, and rosacea. Additionally, 2 IIT studies (1 in plaque psoriasis and 1 in palmo-plantar psoriasis) are onging as of November 2015.

1.6.1. Phase 1 Apremilast Studies

The clinical pharmacology program includes 20 completed studies. In these studies, 716 healthy subjects were exposed to apremilast and 16 subjects with moderate or severe hepatic impairment, 8 subjects with severe renal impairment, 16 subjects with mild to moderate renal impairment, and 15 subjects with PsA or RA were exposed to apremilast. Single doses of apremilast over the dose range of 10 to 80 mg and multiple doses of up to 100 mg/day have been evaluated in Phase 1 studies.

The PK of apremilast in healthy subjects under fasting conditions is characterized by rapid absorption, with Cmax occurring at a median time to maximum concentration (tmax) of approximately 2.5 hours post-dose and an average absolute bioavailability of approximately 73%.

Apremilast demonstrates linear PK, with AUC increasing in a dose-proportional manner through 50 mg BID or 80 mg once daily (QD). In one clinical pharmacology study in subjects with RA or PsA and in five Phase 2 and 3 studies in subjects with PsA, psoriasis, or RA, apremilast exposure was consistent and comparable, although apremilast exposure appeared to be approximately 40% higher in subjects with PsA, psoriasis, or RA versus healthy subjects.

Apremilast is primarily eliminated as metabolites, with less than 3% excreted unchanged in urine. A pharmacologically inactive glucuronide conjugate of O-demethylated apremilast (metabolite M12) is the major circulating metabolite, and its urinary excretion represents approximately 34% of the total administered dose.

Following IV administration, apremilast has a mean total clearance of approximately 10 L/h and a terminal elimination half-life of approximately 6 to 9 hours. Compared to a renal clearance of intact apremilast of 0.1 to 0.3 L/hr, a majority of the total clearance is attributed to metabolic clearance.

A supratherapeutic dose of apremilast 50 mg BID did not prolong the heart rate-corrected QT interval (QTc) in a thorough QT study. Apremilast is therefore not expected to result in clinically significant prolongation of the QT interval at doses up to 50 mg BID.

The inhibition of the CYP3A4 pathway with ketoconazole, a known CYP3A4 inhibitor, resulted in a mean 36% increase in the area under the plasma concentration-time curve from time zero to infinity (AUC_∞) of apremilast. This increase in exposure was not clinically significant. This increase in AUC_∞ in the presence of the inhibition of CYP3A4 by ketoconazole is consistent with the known alternate elimination pathways, hydrolysis in particular, that have been shown for this compound. In healthy subjects, concomitant administration of a standard high-fat breakfast did not have a clinically relevant effect on the systemic exposure of apremilast.

The PK of apremilast is not affected by moderate or severe hepatic impairment; therefore, dose adjustment is not necessary in subjects with hepatic impairment. Apremilast exposure is not affected by mild or moderate renal impairment; therefore, dose adjustment is not necessary in subjects with mild or moderate renal impairment. In subjects with severe renal impairment (< 30 mL/min/1.73 m2), data suggest a 30-mg QD dose produces apremilast exposure comparable to 30 mg BID in subjects without renal impairment; therefore, 30 mg QD is recommended for subjects with severe renal impairment.

1.6.2 Phase 2 and Phase 3 Studies

In the psoriasis studies CC-10004-PSOR-001 and CC-10004-PSOR-004, apremilast treatment was associated with a decrease in dendritic cells and T-cells infiltrating the skin lesions within the epidermis and the dermis. In addition, a significant decrease in inducible nitric oxide synthase (iNOS) gene expression was observed in lesional skin biopsies taken 2, 4, or 12 weeks after treatment initiation. In Study CC-10004-PSOR-001, a decrease in the ability of whole blood to produce TNF-α in response to endotoxin was observed 2 hours after apremilast dosing. In Study CC-10004-PSOR-004, apremilast decreased lesional skin epidermal thickness and expression of

proinflammatory genes, including iNOS, IL-12/IL-23p40, IL-23p19, IL-17A, IL-22, and IL-8. In the PsA study CC-10004-PSA-002, apremilast treatment was associated with a decrease in IL-1α, IL-6, IL-8, MCP-1, macrophage inflammatory protein-1 beta (MIP-1β), TNF-α, matrix metalloproteinase protein-3 (MMP-3), ferritin, and a small increase in von Willebrand factor (vWF) plasma protein levels (note that vWF was within normal range [< 120 µg/mL]). Among these, the decrease in TNF-α and the increase in vWF were significantly associated with meeting the primary endpoint of the study (American College of Rheumatology [ACR] criteria for a 20% improvement [ACR 20] at Week 16). Taken together, these results suggest that partial inhibition of several pro-inflammatory mediators, including iNOS and TNF-α, may play a key role in the mechanism of action of apremilast in the treatment of psoriatic diseases.

In the AS study CC-10004-AS-001, 7 biomarkers had significant differences in percent change from baseline in one or more apremilast groups compared with placebo at more than one time point/analysis method combination: ferritin, intercellular adhesion molecule-1 (ICAM-1), IL-18, IL-8, MIP-1β, osteoprotegerin (OPG), and sclerostin. Percent changes in both IL-8 and MIP-1β were significantly associated with achievement of Assessment of SpondyloArthritis international Society (ASAS) 20 response in the APR 30 BID group.

Two multicenter randomized, double-blind, placebo controlled trials (PSOR-1 and PSOR -2) enrolled a total of 1257 subjects with moderate to severe plaque psoriasis [BSA ≥ 10%, static PGA ≥ 3 (mod to severe disease), PASI score ≥ 12, candidates for phototherapy or systemic therapy]. In both studies, subjects were randomized 2:1 apremilast 30 mg BID or placebo for 16 weeks. Both studies assessed proportion of subjects achieving PASI-75 and proportion of subjects who achieved a sPGA of clear (0) or almost clear (1) at week 16. The mean PASI score pf 19.07 (median 16.80) and proportion of subjects with sPGA score of 3(moderate) or 4 (severe) at baseline were 70.0% and 29.8% respectively. The clinical response is as follows:

	PSOR-1 Placebo	PSOR-1 APR 30 mg BID	PSOR-2 Placebo	PSOR-2 APR 30 mg BID
N[a]	N=282	N=562	N=137	N=274
PASI[b]	15(5.3)	186 (33.1)	8 (5.8)	79 (28.8)
sPGA[c] clear/almost clear, n(%)	11 (3.9)	122 (21.7)	6 (4.4)	56 (20.4)

[a] N is number of randomized and treated subjects
[b] PASI=Psoriasis Area Severity Index
[c] sPGA =Static Physician Global Assessment

1.6.3. Overall Safety

Apremilast is FDA approved for treatment of adult patients with active psoriatic arthritis and for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

In completed and ongoing apremilast Phase 2 or Phase 3 studies, the most commonly observed TEAEs (ie, those reported in > 5% of subjects) have been diarrhea, nausea, headache (including tension headache), upper respiratory tract infections, and nasopharyngitis. The majority of TEAEs of diarrhea, nausea, headache occurred within the first 2 weeks of treatment and most resolved within 4 weeks. The majority of reported TEAEs was mild or moderate in severity and resolved while subjects continued apremilast treatment. The incidence of SAEs was low and comparable between apremilast and placebo treatment groups in the placebo-controlled periods and was not driven by any single preferred term or any specific individual organ toxicity. The safety profile of apremilast is comparable in the psoriasis and PsA indications. The overall safety profile in subjects with AS, BD, and RA is similar to the safety profile in the psoriasis and PsA indications.

As of 30 Nov 2015, 19 deaths have been reported, including 18 deaths in Celgene-sponsored studies and 1 death in an IIT. There is no pattern indicating a causal relationship between death and apremilast treatment.

There was no evidence of an increased risk of major adverse cardiac events (MACE), malignancies, serious infections (including opportunistic infections) or suicidal behavior with apremilast treatment in clinical studies. There were 3 cases of small-vessel cutaneous vasculitis in subjects enrolled in clinical studies: 1 subject with PsA in the APR 30 BID treatment group and 2 subjects with RA (1 subject in the placebo group and 1 subject in the APR 30 BID group).

During a Phase 2 study (CC-10004-PSOR-003), proinflammatory biomarkers did not show evidence of vasculitis with apremilast treatment. Hypersensitivity, with 2 positive rechallenges, was confirmed in 1 subject with PsA in the APR 40 QD treatment group. Apremilast is contraindicated in subjects with known hypersensitivity to apremilast or its excipients. Observed weight loss was associated with apremilast treatment, without overt clinical consequences. A small number of laboratory abnormalities have been classified as adverse events (AEs) in completed and ongoing clinical studies. Most abnormal laboratory findings were not considered clinically significant, did not require medical intervention, and were self-limiting. There were no cases of liver function test (LFT) elevations meeting Hy's Law criteria (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST] > 3 × upper limit of normal [ULN] and bilirubin > 2 × ULN). No clinically significant differences between the placebo and apremilast treatment groups in vital signs or ECG findings have been observed in these studies.

Complete details of contraindications, precautions/warnings, and adverse reactions may be found in the package insert (**see attached**).

1.6.4. Worldwide Approval Status of Apremilast

Apremilast is marketed worldwide under the trade name Otezla®. Apremilast received its first global marketing approval from the Food and Drug Administration in the United States on 21 Mar 2014 for the treatment of adult patients with active PsA. Apremilast is

approved as a treatment for PsA and psoriasis. Apremilast is the first PDE4 inhibitor approved for the treatment of plaque psoriasis and PsA.

As of 30 Nov 2015, apremilast has been approved in 36 countries worldwide.

1.7. Study Rationale

There is no FDA-approved medication for chronic idiopathic pruritus (CIP). Apremilast has demonstrated notable activity and is approved for treatment in other pruritic inflammatory skin conditions such as psoriasis and is currently being investigated for atopic dermatitis. Additionally, we have preliminary data to suggest that apremilast's anti-inflammatory properties may work through its neuromodulatory effects by targetting neuronal cytokine pathways. The proposed study plans to assess the efficacy of apremilast 30 mg BID in the setting of CIP. A durable response to a medication is typically seen within one to two months of starting an efficacious medication in those who respond. Therefore, we have designed this study to end at Week 16 to defintively determine efficacy and conclude the study with confidence with regard to both efficacy and failure.

1.8. Potential Risks and Benefits of the Treatment Regimen

As of 20 Sep 2015 the worldwide exposure to commercial apremilast was approximately 41,244 patients. The safety profile of apremilast in the postmarketing setting remains similar to that observed in the registrational clinical program. The most frequently reported adverse events have been gastrointestinal (diarrhea, nausea, vomiting, abdominal discomfort) and nervous system disorders (headache). There have been no changes required to the Company Core Data Sheet (CCDS) based on postmarketing safety data.

The safety profile of apremilast is comparable in the psoriasis and PsA indications. The most commonly observed TEAEs (ie, those reported in > 5% of subjects) have been diarrhea, nausea, headache (including tension headache), upper respiratory tract infections, and nasopharyngitis.

The majority of the TEAEs of diarrhea, nausea, and headache occurred within the first 2 weeks of treatment, and most resolved within 4 weeks. The majority of reported TEAEs were mild or moderate in severity and resolved while subjects continued apremilast treatment. The incidence of SAEs was low and comparable between apremilast and placebo treatment groups in the placebo-controlled periods and was not driven by any single preferred term or any specific individual organ toxicity. The overall safety profile in the AS, BD, and RA indications is similar to the safety profile in the psoriasis and PsA indications.

The proposed Apremilast 30 mg BID regimen, if successful, will provide an effective therapy for CIP and improve the quality of life in subjects with CIP, a highly debilitating chronic pruritic disorder.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objective(s)

2.1.1. Primary Objective

- To demonstrate that apremilast 30 mg taken orally twice daily (BID) results in improvement in Numerical Rating Scale (NRS) itch score from Baseline.

2.1.2. Secondary Objective

Key Secondary objectives:

- To demonstrate that apremilast 30 mg taken orally twice daily (BID) results in improvement in Dermatology Life Quality Index (DLQI) from Baseline.

2.1.3. Exploratory Objective

- To identify whether skin transcriptomic signatures are altered in response to treatment with apremilast by RNA sequencing (RNA-seq).

2.2. Study Endpoints

2.2.1. Primary Endpoint

- Absolute change in Numerical Rating Scale (NRS) itch score from Baseline to Week 16. The NRS itch score will be recalled from the prior 24 hours first and then the prior 1 week.

2.2.2. Secondary Endpoint(s)

Key secondary endpoints:

- Absolute change in Dermatology Life Quality Index (DLQI) from Baseline to week 16.

Other secondary endpoints:

- Numerical Rating Scale (NRS) itch score at Screening, Baseline, Weeks 2, 4, 8, 12, 16, and 18.
- Dermatology Life Quality Index (DLQI) at Screening, Baseline, Weeks 2, 4, 8, 12, 16, and 18.

- AEs; performing physical examinations; collecting vital signs; and collecting laboratory data for hematology, and serum chemistry.

2.2.3. Exploratory Endpoint(s)

- Skin RNA-seq analysis at Baseline (Week 0) and Week 16.

3. SUBJECT ELIGIBILITY

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

3.1. Subject Inclusion Criteria

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

1. Male and non-pregnant, non-lactating female subjects aged 18 years or older, in good general health (except for disease under study) as judged by the Investigator, based on medical history, PE, clinical laboratories and urinalysis, and absence of uncontrolled significant co-morbidities.
2. Diagnosed with chronic idiopathic pruritus (CIP) with a NRS Itch Score of ≥ 7 at both Screening and Baseline.
3. Diagnosis of CIP for at least 6 weeks prior to screening.
4. Willingness to avoid pregnancy or fathering of children based on the criteria below:
   a. Woman of nonchildbearing potential (surgically sterile with a hysterectomy and/or bilateral oophorectomy OR postmenopausal, defined by last menstrual period for at least 24 months before screening).
   b. Woman of childbearing potential who has a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed. Chosen form of contraception must be effective by the time female subject is randomized.
   c. Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.
5. Ability and willingness to provide written informed consent.
6. Willing and able to comply with all study requirements and restrictions.

7. Willing to not participate in any other interventional trial for the duration of their participation.
8. Subjects must be in good health as determined by past medical history, physical examination, electrocardiogram, clinical laboratory tests and vital signs.
9. Failure of a course 2-week course of treatment with topical triamcinolone 0.1% ointment BID.
10. Histopathological demonstration of dermal edema, skin eosinophils, mast cell activation or lymphocytic infiltration.

3.2. Subject Exclusion Criteria

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

1. Chronic pruritus due to a defined primary dermatologic disorder (e.g., atopic dermatitis, psoriasis, etc.).
2. Patients with a prior diagnosis of excoriation disorder.
3. Use of topical treatments for CIP (other than bland emollients) within 1 week of baseline.
4. Subjects receiving systemic immunosuppressive or immunomodulating drugs (eg, oral or injectable corticosteroids, methotrexate, cyclosporine, mycophenolate mofetil, azathioprine) within 4 weeks of Baseline.
5. Subjects with cytopenias at screening, defined as:
   a. Leukocytes $< 3 \times 10^9$/L
   b. Neutrophils < lower limit of normal
   c. Lymphocytes $< 0.5 \times 10^9$/L
   d. Hemoglobin < 10 g/dL
   e. Platelets $< 100 \times 10^9$/L
6. Unwilling or unable to follow medication restrictions or unwilling or unable to sufficiently washout from use of restricted medication or under treatment for skin disease with therapy listed in prohibited medications that may influence results of this study.
7. Use of any prohibited medications (see Section 5.6.3) within 14 days or 5 half-lives (whichever is longer) of the Baseline visit.
8. Current clinically significant cardiovascular, respiratory, neurologic, hepatic, hematopoietic, renal gastrointestinal, endocrine or metabolic dysfunction unless currently controlled and stable, including (but not limited to) the following:
   a. Positive for hepatitis C antibody test (anti-HCF);
   b. Positive for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb);
   c. Positive for HIV (DUO test, p24 antigen)

9. Active malignancy.
10. History (including family history) or current evidence of congenital long QT syndrome or known acquired QT prolongation.
11. Exposure to any investigational medication, including placebo, within 60 days of the Baseline Visit.
12. History of intolerance and/or hypersensitivity to medications similar to apremilast.
13. Subjects with prior treatment with apremilast.
14. Subjects with severely impaired liver function (Child-Pugh Class C) or end-stage renal disease on dialysis or at least 1 of the following:
    a. Serum creatinine > 1.5 mg/dL;
    b. Alanine aminotransferase or aspartate aminotransferase ≥ 1.5 × upper limit of normal
15. Anyone affiliated with the site or sponsor and/or anyone who may consent under duress.
16. Any other sound medical reason as determined by the Investigator including any condition which may lead to an unfavorable risk-benefit of study participation, may interfere with study compliance or may confound study results.
17. Women who were pregnant or breastfeeding within 4 months before screening.
18. Anyone with prior history of suicide attempt at any time in subject's life prior to screening or randomization or any psychiatric illness requiring hospitalization within last three years.
19. Clinically significant or uncontrolled cardiac disease, including unstable angina, acute myocardial infarction within 6 months from Day 1 of study drug administration, New York Heart Association Class III or IV congestive heart failure, and arrhythmia requiring therapy or uncontrolled hypertension (blood pressure > 150/90 mmHg) unless approved by medical monitor/sponsor.
20. History of alcoholism or drug addiction within 1 year before screening, or current alcohol or drug use that, in the opinion of the investigator, will interfere with the subject's ability to comply with the administration schedule and study assessments.
21. Subjects who anticipate receiving a live or live-attenuated vaccination from screening through the final follow-up visit.
22. Subjects who, in the opinion of the investigator, are unable or unlikely to comply with the administration schedule and study evaluations.

23. Other than disease under study, any clinically significant, as determined by Investigator, cardiac, endocrinologic, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease or other major disease that is currently uncontrolled.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This study is an open label pilot study examining the efficacy of apremilast in the treatment of CIP. Ten (10) subjects who meet the eligibility criteria are planned to be enrolled. The total duration of subject participation will be 6 study visits over approximately 16 weeks. All subjects will receive apremilast 30 mg by mouth BID for 16 weeks.

All apremilast subjects will have visits at Screening, Baseline, and Weeks 2, 4, 8, 12, 16, and 18 (follow-up). Adverse events (AEs), medication history, clinical assessments, physical exam, and vital signs will be performed at each visit. Clinical safety laboratories will be performed at screening and Week 16 (EOT). All laboratory assessments will be performed using The Barnes-Jewish Hospital laboratory except for urine pregnancy tests (as applicable). NRS and DLQI scoring will be performed by a research nurse.

Two skin biopsies will be performed at the most pruritic site at Baseline and at Week 16 (adjacent to the initial biopsy site) for histopathological analysis and RNA-seq transcriptional analysis.

After the end-of-treatment visit (Week 16, or early termination), subjects will have follow-up assessments two weeks later (week 18) to monitor for durability of effect (relapse rate), AEs, medication history, vital signs, and clinical assessments.

4.2. Measures Taken to Avoid Bias

This is an unblinded open label pilot study so the study will be biased for both the subject and the investigator.

4.3. Number of Subjects

The study will include 10 subjects. Discontinued or drop-out subjects will not be replaced.

4.4. Duration of Treatment and Subject Participation

After signing the ICF, screening assessments may be completed over a period of up to 28 days. Scheduled study visits are at Week 2, 4, 8, 12, and 16. Follow up is at Week 18.

Study participation is expected to be approximately 18-22 weeks per individual subject with variance related to screening process duration.

4.5. Overall Study Duration

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

4.6. Study Termination

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

5. TREATMENT

5.1. Treatment Assignment

5.1.1. Subject Numbering and Treatment Assignment

All subjects will be numbered and coded by the study team.

5.1.2. Randomization and Blinding

There will be no randomization nor blinding in this study.

5.2. Apremilast Tablet

5.2.1. Description and Administration

Apremilast 10 mg tablets will be administered at a dose of 30 mg BID. Instructions will be provided with the study medication. The starting dose is 10 mg daily with titration upwards by 10 mg each day until maintainance dose of apremilast 30 mg BID is reached. The titration schedule is as follows:

Day 1: Apremilast 10 mg in am

Day 2: Apremilast 10 mg BID

Day 3: Apremilast 10 mg in am and Apremilast 20 mg in pm

Day 4: Apremilast 20 mg BID

Day 5: Ampremilast 20 mg in am and Apremilast 30 mg in pm

Day 6 and continuing as maintenance: Apremilast 30 mg BID

5.2.2. Supply, Packaging, and Labeling

Apremilast drug product will be provided as Apremilast 10 mg tablets for the titration period. On Day 6, patients will change to 30 mg tablets. All investigational product

labels will be in the local language and will comply with the legal requirements of each country

5.2.3. Storage

Apremilast tablets should be stored between 15°C and 30°C (59°F and 86°F).

5.3. Treatment Compliance

Compliance will be assessed by reviewing the number of tablets remaining at each visit. Subjects will also be questioned regarding study drug use, missing doses, and use of any additional topical or systemic prescriptions of other products or over the counter products. Subjects who are noncompliant with study drug (defined as < 80% compliant based on expected regimen and number of tablets remaining) will have their instructions reinforced by the investigator or a qualified designee. Subjects will be considered compliant with the treatment regimen if they take at least 80% of the expected medications in the treatment phase of the study. Subjects who are noncompliant on more than 1 occasion will be reinstructed by the investigator or a qualified designee, and the sponsor should be consulted by the investigator for instruction on the proper handling of the subject.

5.4. Treatment Interruptions and Adjustments

5.4.1. Dose Modifications

No dose modifications are present in this trial.

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

In some circumstances, it may be necessary to temporarily interrupt treatment as a result of AEs or laboratory abnormalities that may have an unclear relationship to study drug. Decisions on dose interruptions or adjustments will be made by the investigator. Should the subject experience a mild AE or laboratory abnormality, the dose will be reduced to 20 mg BID.

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

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

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

- The subject had a severe drug-related AE as determined by the investigator.

5.4.3. Criteria for Permanent Discontinuation of Study Drug

Subjects who have administration interrupted based on the above criteria will be followed until the parameters return to the normal range or to baseline values. Laboratory evaluations can be repeated as frequently as daily. A subject who has had their dose interrupted based on these criteria may resume administration with study drug at a later time if the subject no longer meets the criteria for interrupting the dose with the sponsor's approval in consultation with the investigator. Subjects who meet withdrawal criteria (**see Section 5.5**) during study drug interruption will be withdrawn from the study and may not resume administration.

5.5. Withdrawal of Subjects From Study Treatment

5.5.1. Withdrawal Criteria

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

- The subject becomes pregnant.
- Consent is withdrawn.
- Further participation would be injurious to the subject's health or well-being, in the Investigator's medical judgment.
- The study is terminated by the local health authority, IRB, or IEC.
- The subject has a dose interruption for >2 weeks

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

- If, during the course of the study, a subject is found not to have met eligibility criteria, the investigator,will determine whether the subject should be withdrawn from the study.
- If a subject is noncompliant with study procedures or study drug administration in the Investigator's opinion.

5.5.2. Withdrawal Procedures

In the event that the decision is made to permanently discontinue the study drug, the subject will be withdrawn from the study and the end-of-treatment visit should be conducted. Reasonable efforts should be made to have the subject return for a follow-up visit. The last date of the last dose of study drug and the reason for subject withdrawal will be recorded in the source document.

If a subject is withdrawn from the study

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

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

5.6. Concomitant Medications

5.6.1. Permitted Medications

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

5.6.2. Restricted Medications and Measures

- Use of any over-the-counter, nonprescription preparations (including vitamins, minerals, and phytotherapeutic, herbal, or plant derived preparations) within 7 days before the baseline visit, unless deemed acceptable by the investigator.
- Use of any prescription medication (including immunizations, phytotherapeutic, herbal, or plant-derived preparations) within 14 days before the baseline visit, unless deemed acceptable by the investigator.
- Use of anti-histamines, doxepin, gabapentin, etc. and other treatments for pruritus should be eliminated at screening.
- Mild-to-moderate CYP3A4 inhibitors will be discouraged from use.

5.6.3. Prohibited Medications and Measures

The following medications are not permitted during the study:

- Any investigational medication other than the study drugs.
- Corticosteroids, topical corticosteroids.
- Other topical agents for chronic pruritus (including topical moisturizers).
- Systemic corticosteroids, methotrexate, cyclosporine A, azathioprine and biological therapies, or other immunosuppressant agents.

- Leukotriene inhibitors, calcineurin inibitors.
- Allergen immunotherapy.
- Phototherapy or tanning beds.
- Live or live-attenuated vaccination.
- Cytochrome 450 enzyme inducers (rifampin, phenobartitol, carbamazepine, phenatoin)

6. STUDY ASSESSMENTS

All study assessments will be performed as indicated in the schedule of assessments **Table 1**, in the order listed, and all laboratory assessments will be performed as indicated in **Table 2**:

Table 1: Schedule of Assessments

Evaluation	Screening	Treatment						Follow-Up	
	Day -28 to -1	Baseline	Week 2 Day 14 ± 3 Days	Week 4 Day 28 ± 3 Days	Week 8 Day 56 ± 3 Days	Week 12 Day 84 ± 3 Days	Week 16 Day 112 ± 3 Days	Week 18 Day 96 ± 3 Days	
Clinic visit	X	X	X	X	X	X	X	X	
Informed consent	X								
Inclusion/exclusion criteria	X	X							
Demography and medical history	X								
Prior/concomitant medications	X	X	X	X	X	X	X	X	
Height and body weight	X								
Comprehensive physical exam	X								
Targeted physical exam(if indicated)		X	X	X	X	X	X	X	
Vital signs and weight	X	X	X	X	X	X	X	X	
Laboratory assessments	X						X		
Chest x-ray	X								
Hepatitis screening tests	X								
Pregnancy test[a]	X	X	X	X	X	X	X	X	
Efficacy assessment (NRS itch score)	X	X	X	X	X	X	X	X	
Derm Quality of Life Index	X	X	X	X	X	X	X	X	
Study drug dispensed/Collect study drug bottles		X	X	X	X	X	X		
Assess compliance			X	X	X	X	X		
Skin biopsy RNA-seq transcriptional profile, and Histopathological analysis		X					X		
Assess AEs	X	X	X	X	X	X	X	X	

[a]All women will have a serum pregnancy test conducted at the screening visit and urine pregnancy tests conducted at all other visits (including baseline) unless postmenopausal (defined as >12 months from last menstrual period) or surgically sterile)

Table 2: Clinical Laboratory Assessments

Serum Chemistries	Hematology
Albumin Alkaline phosphatase ALT AST Bicarbonate Blood urea nitrogen Calcium Chloride Creatinine Glucose Phosphorus Potassium Sodium Total bilirubin Total serum protein	Hematocrit Hemoglobin Mean corpuscular volume Platelet count Red blood cell count Reticulocyte count White blood cell count White blood cell differential (5 part): • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils
Other	**Serology**
ESR Lactate dehydrogenase Urinalysis Urine pregnancy test (at site) Serum pregnancy test TSH	Hepatitis B surface antigen Hepatitis C virus antibody HIV p25 antigen

6.1. Screening

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

Results from the screening evaluations will be reviewed to confirm subject eligibility before administration of study drug. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the results to be in error. Additionally, a subject who fails screening may repeat the screening process one

time if the investigator believes that there has been a change in eligibility status (eg, following recovery from an infection).

6.2. Baseline

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

Subjects who have signed the ICF and meet all the entry criteria may be enrolled in the study.

6.3. Treatment

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

The treatment period begins when the subject receives their first dose of study drug, which will be administered in the clinic. A one month supply will be dispensed to subjects with detailed instructions.

6.4. End of Treatment

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

6.5. Follow-Up

Subjects will have follow-up assessments two weeks after the last dose of study drug. If prohibited treatment for CIP is started, an earlier follow-up visit may be performed. A final and thus end-of-study visit should be performed, ideally no earlier than 14 days after the last dose of study drug. Adverse events and SAEs must be reported up until at least 14 days after the last dose of study drug, the date of the follow-up visit, or until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the subject return for the follow-up visits and report any AEs that may occur during this phase.

6.6. Unscheduled Visits

Unscheduled study visits may occur at any time if medically warranted. Any assessments performed at those visits should be recorded in the source document. If there is worsening of CIP at an unscheduled visit, then NRS and DLQI scores should be obtained and documented.

6.7. Early Termination

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

Subjects who are noncompliant with study drug (defined as < 80% compliant based on number of tablets) will have the administration instructions reinforced by the investigator or a qualified designee. After reinforcement, subjects who again fail to meet 80% compliance benchmarks in a subsequent visit will be considered for withdrawal from the study.

7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

7.1. Administration of Informed Consent Form

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

7.2. Demography and Medical History

7.2.1. Demographics and General Medical History

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

7.2.2. Disease Characteristics and Treatment History

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

7.3. Prior and Concomitant Medications and Procedures

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

7.4. Safety Assessments

7.4.1. Adverse Events

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

7.4.2. Physical Examinations

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

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

7.4.2.1. Comprehensive Physical Examination

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

7.4.2.2. Targeted Physical Examination

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

7.4.3. Vital Signs and Weight

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

7.4.4. Electrocardiograms

N/A.

7.4.5. Laboratory Assessments

Clinical laboratory tests will be performed using a central laboratory. A detailed description of the procedures for sampling, handling, storage, and shipment of the

central laboratory samples and all material such as test tubes and labels is provided in the central Laboratory Manual. If unscheduled local laboratory tests are performed and those results lead to a dose modification, delay, or dose interruption, or any additional non-Protocol–required test is performed because of an AE, those results and the normal reference ranges for those analytes must be documented in the source document. Otherwise, unscheduled local laboratory test results need not be entered in the source document.

Tests required at each visit are shown in Table 1. Additional analytes may be requested based on emerging data, if indicated for safety of study subjects. In addition, some subjects may receive additional assessments as medically indicated; results of nonrequired tests may also be entered in the source document.

7.4.5.1. Chemistry, Hematology and Urinalysis

A panel of standard serum chemistries, hematology, urninalysis will be analyzed at screening and Visit 16 (EOT). All serum chemistries will be performed from blood samples collected without respect to food intake (ie, nonfasting).

7.4.5.2. Hepatitis Screening

Hepatitis test in Table 2 will be conducted during screening period in order to best interpret liver function test abnormalities that may develop during the course of the study. It is therefore not mandatory that this result be available before enrollment (day one) if clinical evaluation and medical history provide not reason to suspect ongoing active or subclinical hepatitis infection.

7.4.5.3. Pregnancy Testing

Pregnancy testing will be performed on all female subjects as noted in the schedules of assessments in **Table 1**. Serum pregnancy test will be obtained at screening. A urine pregnancy test will be obtained all other visits. A positive urine pregnancy test should be confirmed by a serum pregnancy test.

7.5. Efficacy Assessments

7.5.1. Numerical Rating Scale (NRS) Itch Score

The Pruritus NRS is a patient reported measure of itch intensity assessed using an 11-point scale (0 = no itch to 10 = worst imaginable itch). NRS itch scores will be measured at baseline and at every visit to monitor improvement. Furthermore, NRS scores will be obtained for the prior 24 hours, and the week prior in sequential order.

7.5.1.1. Worsening of CIP

If worsening of CIP is present, then NRS scores wil be noted.

7.5.2. Dermatology Life Quality Index (DLQI)

The Dermatology Life Quality Index or DLQI, developed in 1994, was the first dermatology-specific Quality of Life (QOL) instrument. It is a simple 10-question validated questionnaire that has been used in over 40 different skin conditions in over 80 countries and is available in over 90 languages. Its use has been described in over 1000 publications including many multinational studies. The DLQI is the most frequently used instrument in studies of randomised controlled trials in dermatology. The DLQI 10-question validated questionnaire to measure quality of life impact and will be measured at Baseline and at every visit (see Appendix B).

7.6. Skin Biopsy Analysis: RNA Seq Analysis and Histology

Skin biopsy analysis will be used to investigate molecular signatures associated with response or resistance to treatment with the study drug. Ribonucleic acid (RNA) will be extracted from these samples to perform RNA-seq analysis that may include genome-wide gene expression profiling. The tissue will also be examined histopathologically.

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definitions Adverse Events and Serious Adverse Events

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence occurring at any dose that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any medical condition that was present prior to study treatment and that remains unchanged or improved should not be recorded as an AE. If there is a worsening of that medical condition this should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the Case Report Form rather than the individual signs or symptoms of the diagnosis or syndrome.

All AEs will be recorded by the Investigator(s) from the time of signing the informed consent through the end of the designated follow-up period.

Abnormal laboratory values defined as adverse events

An abnormal laboratory value is considered to be an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study.

- Requires treatment, modification/interruption of study drug dose, or any other therapeutic intervention.
- Is judged by the Investigator(s) to be of significant clinical importance.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

Serious adverse event

A serious adverse event (SAE) is any AE which:

- Results in death
- Is life-threatening (i.e., in the opinion of the Investigator(s) the subject is at immediate risk of death from the AE)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions)
- Results in a congenital anomaly/birth defect
- Constitutes an important medical event

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events not considered to be SAEs are hospitalizations which: were planned before entry into the clinical study; are for elective treatment of a condition unrelated to the studied indication or its treatment; occur on an emergency outpatient basis and do not result in admission (unless fulfilling other criteria above); are part of the normal treatment or monitoring of the studied indication and are not associated with any deterioration in condition.

If an AE is considered serious, both the AE pages of the CRF and the SAE Report Form must be completed.

For each SAE, the Investigator(s) will provide information on severity, start and stop dates, relationship to study drug, action taken regarding study drug, and outcome.

Classification of severity

For both AEs and SAEs, the investigator(s) must assess the severity of the event. The AEs will be evaluated for severity according to the following scale:

Grade 1 = Mild

Grade 2 = Moderate

Grade 3 = Severe

Classification of Relationship/Causality of adverse events (SAE/AE) to study drug

The Investigator(s) must determine the relationship between the administration of study drug and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected: The temporal relationship of the adverse event to study drug administration makes a causal relationship unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event

Suspected: The temporal relationship of the adverse event to study drug administration makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed even

8.2. Reporting Serious Adverse Events: Immediate

Any AE that meets the any criterion for a SAE requires the completion of an SAE Report Form in addition to being recorded on the AE pages of the CRF. The Investigator(s) is required to ensure that the data on these forms is accurate and consistent. This applies to all SAEs, regardless of relationship to study drug, that occur during the study, those made known to the Investigator(s) within 30 days after a subject's last dose of study drug, and those made known to the investigator(s) at anytime that are suspected of being related to study drug. The SAE must be reported immediately (i.e., within 24 hours of the Investigators' knowledge of the event) to Celgene Safety by facsimile. A written report (prepared by the Investigator(s) using an SAE Report Form or a 3500A Medwatch form is to be faxed to Celgene Drug Safety.

Celgene Drug Safety Contact Information:

Celgene Corporation, Global Drug Safety and Management
86 Morris Ave Summit, NJ 07901

FAX (908) 673-9115 EMAIL drugsafety@celgene.com

The SAE report should provide a detailed description of the SAE. If a subject has died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene as soon as these become available. Any follow-up data will be detailed in a subsequent SAE Report Form or Medwatch form and sent to Celgene.

The Investigator(s) is responsible for informing the Institutional Review Board/Ethics Committee (IRB/IEC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator(s) must keep copies of all

SAE information, including correspondence with Celgene and the IRB/IEC, on file. All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until either the event resolves completely, stabilizes/resolves with sequelae, or returns to baseline (if a baseline value is available).

8.3. Pregnancy

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject or the female partner of a male subject occurring while the subject is on study drug, or within 30 days of the subject's last dose of study drug, are considered immediately reportable events. Study drug is to be discontinued immediately and the subject instructed to return any unused portion of the study drug to the investigator(s). The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Safety immediately facsimile using the Pregnancy Report form provided by Celgene.

The female should be referred to an obstetrician-gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The Investigator(s) will follow the female subject until completion of the pregnancy, and must notify Celgene Safety of the outcome of the pregnancy as a follow-up on the follow up Pregnancy Reporting form.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the Investigator(s) should follow the procedures for reporting SAEs (i.e., report the event to Celgene Safety by facsimile within 24 hours of the Investigator's knowledge of the event).

In the case of a live "normal" birth, Celgene Safety should be advised by facsimile within 24 hours of the Investigator's knowledge of the event.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator(s) suspects is related to the in utero exposure to the study drug should also be reported to Celgene Safety by facsimile within 24 hours of the Investigators' knowledge of the event.

If the female is found not to be pregnant, any determination regarding the subject's continued participation in the study will be determined by the Investigator.

8.4. Overdose

Abuse, withdrawal, sensitivity, or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated

with an AE should be reported as an AE. Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE.

If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form but should not be reported as an SAE itself.

In the event of an overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for apremilast overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

Overdose for this protocol, on a per dose basis, is defined as ingestion of any more than the amount prescribed of apremilast (or matching placebo) tablets in any 24 hour period whether by accident or intentionally.

8.5. Data Monitoring Committee

No external data monitoring committee will be used, however, safety data will be monitored throughout the study directly by the investigator and the study team.

8.6. Product Complaints

The investigator is responsible for reporting a complete description of the product complaint via email or other written communication to Celgene as noted in the packaging information. Any AE associated with a product complaint should be reported as described in Section 8.2 of this Protocol.

9. STATISTICS

9.1. Study Populations

The intent-to-treat (ITT) population includes all subjects enrolled into the trial.

The per protocol (PP) population includes all subjects who are considered to be sufficiently compliant with the Protocol.

The safety evaluable population includes all subjects who applied at least 1 dose of study drug. Treatment groups for this population will be determined according to the actual treatment the subject received on Day 0.

9.2. Selection of Sample Size

The same patient will be compared at two time points therefore we will perform a paired t-test analysis of the NRS itch score. However, we will also have additional visits in between the two time points therefore we will have additional data points that can be further incorporated for more extensive statistical analyses. All patients will start at a high NRS score of 7 or greater there will be very little variability in the initial study population. Based on a random sampling of 10 patients with CIP in our clinic with histpathologic findings of dermal edema, eosinophil infiltration, mast cell activation and/or lymphocytic infiltration, we identified a mean NRS score of 8.8 with a standard deviation of 1.1. The NRS scale runs from 0 to 10 thus any significant decrease in our NRS score will be captured with even a small sample size. N = 10 should be more than sufficient based on this amount of variance and starting NRS score.

9.3. Level of Significance

We aim to reach statistical significance with our current design of a *P*-value of 0.05 or lower. If we do not, but observe a strong trend, we will perform power calculations to determine what level of enrollment would require the detection of a statistically significant effect.

9.4. Statistical Analyses

9.4.1. Efficacy Analyses

9.4.1.1. Efficacy Measures for Primary and Secondary Endpoints

9.4.1.1.1 Numerical Rating Scale (NRS) itch score

Numerical Rating Scale (NRS) itch score is a single-question assessment tool with a scale of 0-10, with 0 being 'no itch' and 10 'worst itch imaginable'. The average NRS itch score will be measured overall, for the prior 24 hours first and then the prior one week. The NRS itch score improvement will be calculated relative to baseline at each visit. The primary endpoint is the change from baseline in NRS at Week 12.

9.4.1.2.1 Dermatology Life Quality Index (DLQI)

The DLQI score improvement will be calculated relative to baseline at each visit. The key secondary endpoint is the change from baseline in DLQI at Week 12.

9.4.1.2. Statistical Methods

Subjects will be compared at two time points, a paired t-test analysis of the NRS itch score will be performed. However additional visits in between the two time points will have additional data points that can be further incorporated for the more extensive statistical analyses. As all subjects will start at a high NRS score (greater than or equal to 7) there will be very little variability in the initial study population. Based on randam sampling of 10 patients with CIP in our itch clinic, we identified a mean NRS score of 8.8 with a standard deviation of 1.1. Therefore, any significant decrease will be

captured with a small sample size. Based on this amount of variance and starting NRS score, n = 10 is sufficient.

9.4.2. Safety Analyses

9.4.2.1. Adverse Events

A treatment-emergent adverse event (TEAE) is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study drug administration.

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

9.4.2.2. Clinical Laboratory Tests

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

9.4.2.3. Vital Signs

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

9.4.3. RNA seq Analysis

Skin gene expression signatures will be performed at baseline and Week 12 to identify RNA signatures associated with treatment response.

10. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

10.1. Investigator Responsibilities

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

The investigator will be responsible for:

- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and subject records at each monitoring visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all subjects.
  - Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.
- Obtaining informed consent and ensuring that the study subjects' questions have been answered and the subjects fully understand study procedures:
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.
  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the subject. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to subject records.
- Obtaining approval from the IRB/IEC before the start of the study and for any changes to the clinical study Protocol, important Protocol deviations, routine updates, and safety information in accordance with institutional requirements and local law.
  - The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by the IRB/IEC.
- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its

designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling subjects who have met the specified eligibility criteria.

- Retaining records in accordance with all local, national, and regulatory laws, but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.
  - All source document data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original source document data and audit trail.

10.2. Accountability, Handling, and Disposal of Study Drug

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

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

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

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until verified by the study monitor (unless otherwise agreed to

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

10.3. Data Management

The investigator and the research team will maintain all source documents for each subject. The investigator will be responsible for reviewing all data and source document entries, and will sign and date the designated forms in each subject's source document, verifying that the information is true and correct. The investigator is responsible for the review and approval of all query responses.

Protocol deviations will be identified and recorded in the Protocol Deviation form of the source document. The investigator ensure that each issue identified is appropriately documented, reported, and resolved in a timely manner.

10.4. Data Privacy and Confidentiality of Study Records

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

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

10.5. Financial Disclosure

Before study initiation, all clinical investigators participating in clinical studies subject to FDA Regulation Title 21 Code of Federal Regulations (CFR) Part 54 – Financial Disclosure by Clinical Investigators (ie, "covered studies") are required to submit a completed Clinical Investigator Financial Disclosure form that sufficiently details any financial interests and arrangements that apply. For the purpose of this regulation,

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

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

10.6. Publication Policy

Study results will be published in accordance with applicable local and national regulations. The terms regarding the publication of study results are contained in the agreement signed with the sponsor or its designee. A signed agreement will be retained by the sponsor or its designee.

11. REFERENCES

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APPENDIX A. CONTRACEPTIVE METHOD INFORMATION

For Subjects Participating in the Study:

The risks to a fetus or to a nursing child from apremilast are not known at this time. Results of the animal and in vitro studies can be found in the IB. All females of childbearing potential (FCBP) must use one of the approved contraceptive options while on investigational product and for at least 28 days after administration of the last dose of the investigational product. The following methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods.

Such methods include:

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

Male subjects (including those who have had a vasectomy) who engage in activity in which conception is possible must use barrier contraception (male latex condom or nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane]) while on investigational product and for at least 28 days after the last dose of investigational product.

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.

[2] Contraception methods that in the context of this guidance are considered to have low user dependency.

[3] Vasectomised partner is a highly effective method provided of avoiding pregnancy that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

[4] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

APPENDIX B. DERMATOLOGY LIFE QUALITY INDEX (DLQI)

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ➔ 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 skin?

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 ❒

4. 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 ❒

5. Over the last week, how much has your skin affected any **social** or **leisure** activities?

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

6. 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 ❒

7. Over the last week, has your skin prevented you from **working** or **studying**?

Yes ❒
No ❒ Not relevant ❒

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 ❒

8. 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 ❒

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

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

10. 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 ❒

Please check you have answered EVERY question. Thank you.