Study Title:	**A Randomized, Double-Blind, Placebo-Controlled, Multicenter, 24-Week Study to Assess the Efficacy and Safety of PPC-06 (Tepilamide Fumarate) Extended Release Tablets in Subjects with Moderate-to-Severe Plaque Psoriasis (AFFIRM Study)**
Drug Name/Dosage:	PPC-06/400 mg QD, 400 mg BID, 600 mg BID
Protocol No:	PPC-06-CD-004
IND No:	120973
Development Phase:	2
Document Status, Date:	26 October 2018
Document Version:	V3.0, Amendment 2
Previous Version:	V2.0, Amendment 1, 30 May 2018 Original Protocol 25 October 2017
Sponsor:	Dr Reddy's Laboratories, SA Elisabethenanlage 11 CH-4051 Basel Switzerland
Sponsor Agent:	Dr Reddy's Laboratories, Inc. 107 College Road East Princeton, NJ 08540

SIGNATURE PAGE

Product: **PPC-06 (Tepilamide Fumarate) Extended Release Tablets**

Protocol number: **PPC-06-CD-004**

The signatures of the representatives below constitute their approval of this protocol and provide the necessary assurances that this study will be conducted according to all stipulations stated in the protocol, including all statements as to confidentiality. It is also agreed that the study will not be initiated without the approval of an appropriate Institutional Review Board or Ethics Review Committee.

Signatures:

Sagar Munjal
Vice President, Clinical Development
Dr. Reddy's Laboratories

Signature — Date: 10/29/18

Usha Ranganathan
Associate Director, Clinical Development
Dr. Reddy's Laboratories

Signature — Date: 29 Oct 2018

Jin Wei
Associate Director
Biostatistics
Novella Clinical

Signature — Date: 10/29/18

SIGNATURE PAGE FOR INVESTIGATOR(S)

Product: **PPC-06 (Tepilamide Fumarate) Extended Release Tablets**

Protocol Number: **PPC-06-CD-004**

Protocol Title: **A Randomized, Double-Blind, Placebo-Controlled, Multicenter, 24-Week Study to Assess the Efficacy and Safety of PPC-06 (Tepilamide Fumarate) Extended Release Tablets in Subjects with Moderate-to-Severe Plaque Psoriasis**

The signature of the study investigator below constitutes his/her approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations, clinically and administratively, as detailed in the protocol. It is agreed that the conduct and results of this study will be kept confidential.

COMPLIANCE STATEMENT

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46; 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312) and ICH E6; 62 Federal Register 25691 (1997).

SIGNATURES

The signatures below provide the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator's printed name

Principal Investigator's signature

Date

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine transaminase
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
Anti-HBc	Antibody to hepatitis B virus core antigen
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical Classification System
BDM	Biostatistics and Data Management Group
BID	Twice a day
BMI	Body mass index
BSA	Body surface area
BUN	Blood urea nitrogen
CRO	Contract Research Organization
CXR	Chest x-ray
DLQI	Dermatology Life Quality Index
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (version 5)
DMF	Dimethyl fumarate
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessments
eCRF	Electronic Case Report Form
EOS	End of study
ER	Extended release
ETV	Early termination visit
EU	European Union
FAE	Fumaric acid ester
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HBc	Hepatitis B virus core antigen
HbsAg	Surface antigen of the hepatitis B virus
HCP	Healthcare professional
HCV	Hepatitis C virus
HDL	High density lipoprotein

Abbreviation	Definition
HEOR	Health Economics and Outcomes Research
HIV	Human immunodeficiency virus
hsCRP	High-sensitivity C reactive protein
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IP	Investigational product
IGA	Investigator's Global Assessment
IRB	Institutional Review Board
IL2	InfoLink2
IXRS	Interactive voice and web response system
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LLN	Lower limit of normal
LOCF	Last observation carried forward
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCMC	Markov Chain Monte Carlo method
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MEF	Monoethyl fumarate
MI	Multiple imputation
MMF	Monomethyl fumarate
MMRM	Mixed model for repeated measures
mNRI	Modified non-responder imputation
MTX	Methotrexate
NAPSI	Nail Psoriasis Severity Index
NRS	Numeric rating scale
OC	Observed-cases
OTC	Over-the-counter
PASI	Psoriasis Area and Severity Index
PASI-50	At least 50% reduction in PASI score
PASI-75	At least 75% reduction in PASI score
PD	Pharmacodynamic(s)
PDS	Protocol deviation specification
PGA	Physician's Global Assessment
PML	Progressive multifocal leukoencephalopathy

Abbreviation	Definition
PP	Per protocol
PP PGA	Palmoplantar Psoriasis Physician's Global Assessment
PSSI	Psoriasis Scalp Score Index
PT	Preferred Term
PUVA	Psoralen and ultraviolet A
QD	Once daily
QIDS-SR16	Quick Inventory of Depressive Symptomatology-Self Report (16 Items)
QoL	Quality of Life
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SF-12	12-item Short Form Survey
SOC	System Organ Class
sPGA	Static physician's global assessment
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
UPT	Urine pregnancy test
US	United States
UV	Ultraviolet
VAS	Visual analog scale
WBC	White blood cell
WNL	Within normal limits
WPAI:PSO	Work Productivity and Activity Impairment Questionnaire: Psoriasis

1. SYNOPSIS

Study Title:	A Randomized, Double-Blind, Placebo-Controlled, Multicenter, 24-Week Study to Assess the Efficacy and Safety of PPC-06 (Tepilamide Fumarate) Extended Release Tablets in Subjects with Moderate-to-Severe Plaque Psoriasis
Protocol Number:	PPC-06-CD-004
Sponsor:	Dr. Reddy's Laboratories, SA
Development Phase:	2
Study Objectives:	Co-primary objectives: 1. To demonstrate the efficacy of PPC-06 with respect to Psoriasis Area and Severity Index (PASI) for the treatment of moderate-to-severe plaque psoriasis, as compared to placebo at 24 weeks 2. To demonstrate the efficacy of PPC-06 with respect to Investigator's Global Assessment (IGA) at 24 weeks Secondary objectives: 1. To assess the efficacy of PPC-06 as it relates to psoriasis-related symptoms and health-related quality of life (QoL) measures 2. To assess the safety and tolerability of PPC-06 in subjects with moderate-to-severe plaque psoriasis 3. To evaluate the pharmacodynamics (PD) of PPC-06 through immunological analysis of peripheral blood samples.
Study Design:	This is a randomized, double-blind, placebo-controlled, multicenter study designed to assess the safety and efficacy of PPC-06 (tepilamide fumarate) extended release [ER] tablets in subjects with moderate-to-severe plaque psoriasis. Study subjects will be enrolled at approximately 75 sites in the United States (US). The study will be comprised of 4 study periods: 1) Screening Period, 2) Double-Blind Titration Period, 3) Double-Blind Treatment Period, and 4) Post-treatment Follow-Up Period. Following completion of the pre-randomization Screening Period (up to 4 weeks), approximately 400 eligible subjects will be randomly assigned in a 1:1:1:1 ratio to one of the 4 arms (PPC-06 400 mg QD, PPC-06 400 mg BID, PPC-06 600 mg BID, or placebo BID) and the subjects will enter the 5-week Double-Blind Titration Period. At Visit 3 (Week 4), the subjects will continue 1 more week of titration dose (Week 5 of blister wallets) and will also be given a kit of bottles which will allow dosing until Visit 4 (Week 8). Subjects will receive double-blind treatment from Week 6 through Week 24. Subjects will return to the clinic every 4 weeks (±3 days) thereafter, until Week 24, for drug accountability and to undergo safety and efficacy evaluations. Subjects will return at Week 25 for an End of Study (EOS) Safety Follow-Up Visit. There are 9 expected visits total per subject. Blood samples for pharmacodynamics (PD) assessments will be collected at Baseline and at Weeks 4, 8, 12, 16, 20, and 24. PD assessments will be conducted for all subjects, with the intent of evaluating psoriasis-associated inflammatory markers. Details of PD assessment will be provided in a separate protocol. The Early Termination Visit (ETV) will be scheduled if the study drug is permanently discontinued for any reason (for example: due to meeting the protocol-mandated safety monitoring criteria or unresolved gastrointestinal [GI]-related intolerability).

	The EOS Safety Follow-up Period will consist of 1 visit 1-week (± 3 days) following the Week 24 Visit or the ETV. In the event that the Week 24 Visit or the ETV occurs > 1 week following the last dose of the study drug, the EOS Safety Follow-up Visit may not be required. The ETV and/or EOS Safety Follow-Up Visit are not expected to be completed for subjects who withdraw full consent or are lost to follow up. If necessary, the Investigator may decide to extend the follow-up visits beyond 1 week to monitor recovery of safety parameters (e.g., lymphopenia).
Planned Sample Size:	Approximately 400 subjects (~100 subjects per treatment arm)
Study Population:	**Inclusion criteria:** Subjects must meet all of the following criteria to be eligible for participation in the study: 1. Generally healthy males or non-pregnant females age ≥18 years at the time of screening (or who have reached the state minimum legal age of consent). 2. Stable, moderate-to-severe plaque psoriasis diagnosed for at least 6 months prior to randomization (no morphology changes or significant flares of disease activity in the last 6 months in the opinion of the investigator or as reported by the subject). 3. Severity of disease meeting all 3 of the following criteria prior to randomization (at the Baseline [Day 0] visit): a. PASI score of ≥12 b. Total body surface area (BSA) affected by plaque psoriasis of ≥10% c. IGA score of ≥3 4. Must be a candidate for phototherapy and/or systemic therapy for psoriasis. 5. Ability to independently travel to study center and to comply with all study medication and procedures or identification of a caregiver committed to assuring compliance with those study related activities. 6. Able to understand and have voluntarily signed an informed consent form (ICF) prior to undergoing any study-specific procedures. 7. Women of child-bearing potential must have had a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test (UPT) at Baseline prior to randomization. 8. Heterosexual female subjects of childbearing potential must agree to use contraception during the study which can include abstinence with an adequate secondary option should the subject become sexually active. All women of childbearing potential must complete a urine pregnancy test at the baseline visit and the test must be negative to be eligible for enrollment. (Test must have a sensitivity of at least 25 mIU/mL for human chorionic gonadotropin). A female is considered of childbearing potential unless she is a) postmenopausal for at least 12 months prior to study product administration b) without a uterus and/or both ovaries; or has been surgically sterile (i.e., tubal ligation) for at least 6 months prior to study product administration. Reliable methods of contraception are: a) hormonal methods or intrauterine device in use ≥ 90 days prior to study product administration or barrier method plus spermicide in use at least 14 days prior to study product administration or partner has had a vasectomy at least 3 months prior to study product administration or Essure®. **Exception:** Sexually inactive female subjects of childbearing potential are not required to practice a reliable method of contraception and may be

	enrolled at the investigator's discretion provided that they are counseled to remain sexually inactive for the duration of the study and understand the possible risks involved in getting pregnant during the study. An abstinent heterosexual female must agree that if she becomes sexually active during the study she will use an acceptable form of contraception 9. Willing to avoid excessive sun exposure/tanning during the study. Note: If a subject does not meet the inclusion criteria in terms of PASI, total BSA, and/or IGA at Screening, but in the opinion of the Investigator, the subject could meet the inclusion criteria related to PASI, total BSA, and IGA at the Baseline Visit, the subject can be scheduled for the Baseline Visit where these eligibility criteria as well as all other inclusion/exclusion criteria must be met before the subject can be randomized into the study. **Exclusion Criteria:** Any of the following will be regarded as a reason for exclusion from the trial: 1. Subjects with non-plaque psoriasis (ie, predominantly inverse, erythrodermic, predominantly guttate, or pustular psoriasis). 2. Subjects with drug-induced psoriasis or subjects with drug-exacerbated psoriasis that has not resolved within 4 weeks prior to screening. 3. Subjects who have received systemic non-biologic psoriasis therapy or phototherapy (including either oral and topical psoralen and ultraviolet A (PUVA) light therapy, ultraviolet B, or self-treatment with tanning beds or therapeutic sunbathing) within 4 weeks prior to the Baseline Visit. Subjects who had topical psoriasis treatment within the previous 2 weeks prior to the Baseline Visit. Exceptions: Mild/least potent topical steroids will be permitted for use limited to the face, axilla, and/or genitalia. Medicated shampoos containing the active ingredients zinc pyrithione, salicylic acid, selenium sulfide, or ketoconazole will be permitted for use in the shower on the scalp only. 4. Subjects with history of concurrent or recent use of any biologic agent within the following washout periods prior to baseline visit: • Etanercept – 35 days • Infliximab, adalimumab - 12 weeks • Ustekinumab – 24 weeks • Any other biologic agent <5 half-lives prior to the Baseline Visit Note 1: Screening visit can be extended on case-by-case basis (but no more than additional 4 weeks) to complete the wash out. Note 2: A maximum of 30% of subjects with prior biologic use (ie, subjects who received systemic biologic drugs in the past) will be enrolled, but they must be washed out prior to randomization. 5. Subjects with prior exposure to natalizumab, rituximab, or belilumab in the past 1 year prior to screening visit. 6. Subjects with history of use of any investigational drug within 28 days prior to randomization, or 5 pharmacokinetic/ pharmacodynamic half-lives (whichever is longer). 7. Subjects who have failed on 3 or more systemic therapies.

	8. Subjects who cannot avoid excessive sun exposure or use of tanning booths for at least 4 weeks prior to the Baseline Visit and during the day for the entire duration of the study. 9. Subjects with unstable or significant illness, including the presence of laboratory abnormalities or electrocardiogram (ECG) abnormalities, at screening that, in the opinion of the Investigator, would place the subject at unacceptable risk if he/she were to participate in the study (eg, clinically significant abnormality on ECG, any other auto-immune conditions where subject is on immunosuppressive agents). 10. Subjects with sarcoidosis, active tuberculosis, or incompletely treated tuberculosis (TB), or any other serious systemic infection. 11. Any skin condition (eg, eczema) that would confound the ability to interpret data from the study. 12. Subjects whose BMI is >39. 13. Subjects with a present or past history of any major neurological conditions such as stroke, transient ischemic attack, seizures, cranial nerve palsies, major head trauma, brain tumor, demyelinating disorders. 14. Subjects with a current history of any medical condition associated with significant gastrointestinal (GI) events such as nausea, vomiting, constipation, abdominal pain, or diarrhea, which in the opinion of the investigator would affect the tolerability of the drug. 15. Subjects with severe gastritis, duodenal ulcer, severe symptomatic lactose intolerance, irritable bowel syndrome, present or a past history of inflammatory bowel disease or severe dysphagia. 16. Subjects with a persistent history (more than 3 consecutive months) of lymphopenia (below the lower limit of normal [LLN]) in the last 2 years. 17. Subjects who had prior treatment with dimethyl fumarate (Fumaderm® or Tecfidera®) or any other fumaric acid ester (FAE) containing products. 18. Subjects who at Screening and/or randomization have uncontrolled high blood pressure values, which, in the opinion of the Investigator, may increase the risk of cardiovascular events. 19. Subjects who at Screening have creatinine clearance <60 mL/min. 20. Subjects who, according to the Reference Laboratory Manual, at Screening have: a. White blood cells (WBC) < 3000/mm³ b. Neutrophils/granulocytes less than the LLN c. Platelets <110,000/ mm³ d. Lymphocytes <1000/mm³ e. Serum creatinine >1.5× the upper limit of normal (ULN) f. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2×ULN g. Significant proteinuria measured as 3+ or above in urine dipstick in two samples taken on two different days h. Non-fasted blood glucose > 200mg/dL Note: Laboratory tests that cross these thresholds can be repeated once if the Investigator has a clinical reason to believe that a result may be erroneous in which case the laboratory result should be discussed and agreed with the Medical Monitor before repeating it. The repeat value can be accepted if it meets protocol criterion.

	Subjects who have chronically abnormal laboratory values beyond any of the above exclusionary thresholds are excluded even if they are deemed clinically normal. 21. Subjects who had positive results at Screening for hepatitis B (HBsAg and anti-HBc), hepatitis C, or human immunodeficiency virus (HIV). 22. Subjects who have a known immunodeficiency, receive immune modulatory/immune suppressant therapy, or are immunocompromised. 23. Subjects with malignancy (except for adequately treated basal cell carcinoma, squamous cell carcinoma and carcinoma in situ of the cervix) or subjects with history of malignancy, with evidence of recurrence within the previous 5 years. 24. Subjects with a history of drug or alcohol use disorder based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria (within the 6 months prior to screening) as reported by the subject or known to the Investigator. 25. Subjects with cognitive deficit or psychiatric syndrome of any etiology that may influence compliance with study procedures or study outcome. 26. Subjects with a history of allergy to any component of the study drug. 27. Women who are lactating or breastfeeding. 28. Investigator site personnel directly affiliated with this study and/or their immediate families. 29. Sponsor employees or its designee or employees of third-party organizations involved in the study. 30. Prisoners or subjects who are involuntarily incarcerated.
Investigational Product(s):	PPC-06 (tepilamide fumarate) Extended Release Tablets for oral administration: 400 mg QD regimen, 400 mg BID regimen, 600 mg BID regimen, or Placebo BID regimen. A 5-week Double-Blind Titration Period will be followed by a 19-week Double-Blind Treatment Period.
Reference Product(s):	Not applicable
Control Product(s):	Placebo tablets for oral administration to match PPC-06 Extended Release Tablets
Efficacy Evaluation Criteria:	Efficacy assessments include the PASI, the affected BSA, and the IGA. Health-related QoL assessments include the Quick Inventory of Depressive Symptomatology-Self Report (16 Items) (QIDS-SR16), the Dermatological Life Quality Index (DLQI), the 12-item Short Form Survey (SF-12), the Work Productivity and Activity Impairment Questionnaire: Psoriasis (WPAI:PSO), and evaluation of Health Economics and Outcomes Research (HEOR). Other assessments (for subjects with psoriasis in the relevant areas) include the Nail Psoriasis Severity Index (NAPSI), the Psoriasis Scalp Score Index (PSSI), the Palmoplantar Psoriasis Physician's Global Assessment (PP PGA) score, and the Pruritus Numerical Rating scale (NRS). PD assessments would include immunological analysis of peripheral blood samples. Details of PD assessment will be provided in a separate protocol.
Pharmacokinetics Evaluation Criteria:	Not applicable
Safety Evaluation Criteria:	Adverse event (AE) incidence and severity, laboratory test results (hematology, clinical chemistry, urinalysis), vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate), physical examination, ECGs, and pregnancy testing.

Efficacy Endpoints	The co-primary efficacy endpoints will be the proportion of subjects who achieve a reduction of 75% or greater from Baseline PASI (PASI-75) at the end of Week 24 and the proportion of subjects who achieved an IGA score of clear or almost clear (IGA 0, 1) at the end of Week 24. Secondary efficacy endpoints include the following: • Change from Baseline and percent change from Baseline in total PASI score at each visit in the Double-Blind Treatment Period • The proportion of subjects who achieve PASI-50 and PASI-75 at each visit in the Double-Blind Treatment Period • The proportion of subjects who achieved an IGA score of clear or almost clear at each visit in the Double-Blind Treatment Period • The change from Baseline and percent change from Baseline in percent of affected BSA at each visit in the Double-Blind Treatment Period • Mean change in the NAPSI of the target fingernail (score range 0-8) from Baseline at Weeks 12, 16 and 24 in the target fingernail with the most severe abnormalities for those who present with lesions in nails at baseline • Mean change in the PSSI score from Baseline at each visit in the Double-Blind Treatment Period for those that present with lesions on scalp at baseline • Mean change in the Palmoplantar Psoriasis Physician's Global Assessment (PP PGA) score from Baseline at each visit in the Double-Blind Treatment Period for those that present with lesions on the palms/soles at baseline • The change from Baseline and percent change from Baseline in pruritus NRS score at each visit in the Double-Blind Treatment Period • Time to achieving a PASI-75 response, defined as time in days from baseline to first achieving a reduction of 75% or greater from Baseline in PASI • Time to achieving an IGA score of clear or almost clear, defined as time in days from baseline to first achieving an IGA score of 0 or 1 Health-related QoL assessments include: • QIDS-SR16 total score • DLQI total score • SF-12 total score • WPAI:PSO score • HEOR evaluation **Safety Endpoints**: Safety will be assessed through the monitoring of AEs, laboratory test results, vital signs, physical examinations, pregnancy testing and ECGs.
Study Sites:	Approximately 75 study sites in the US
Planned Dates of Study:	November 2017 to January 2019

Table 1-1 Visit Schedule and Assessments

Evaluation	Screening Period[1]	Double-Blind Titration Period (5 weeks)		Double-Blind Treatment Period					ETV and EOS Safety Follow-up Period[2]		Un-scheduled Visit[3]
	Weeks -4 to 0	Baseline visit	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Early Termin-ation Visit	Week 25 (1 Week AfterWeek 24/ETV)	
Study Day	**Day -28 to Day -1**	**Day 0**	**Day 28** (± 3 days)	**Day 56** (± 3 days)	**Day 84** (± 3 days)	**Day 112** (± 3 days)	**Day 140** (± 3 days)	**Day 168** (± 3 days)	**-**	**175 (+3 days)**	
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**ETV**	**9**	**UNS**
Informed Consent	X										
Inclusion/Exclusion Criteria	X[4]	X[5]									
Demographics	X										
Psoriasis Medical History/Prior Psoriasis Therapies	X	X									
Other Medical History/Prior Meds	X	X									
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Washout of Prohibited Meds	X										
Confirm washout of prohibited meds		X									
Study Process / Study Drug Dispensation											
Randomization		X									
Study Drug Dispensing		X[6]	X	X	X	X	X				
Drug Accountability/ Compliance			X	X	X	X	X	X	X		
Collect Baseline stool consistency using Bristol Stool Chart		X									
Dispense Educational Materials for AE Management		X									
Safety Assessments											

Evaluation	Screening Period[1]	Double-Blind Titration Period (5 weeks)		Double-Blind Treatment Period					ETV and EOS Safety Follow-up Period[2]		Un-scheduled Visit[3]
	Weeks -4 to 0	Baseline visit	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Early Termin-ation Visit	Week 25 (1 Week AfterWeek 24/ETV)	
Study Day	**Day -28 to Day -1**	**Day 0**	**Day 28** (± 3 days)	**Day 56** (± 3 days)	**Day 84** (± 3 days)	**Day 112** (± 3 days)	**Day 140** (± 3 days)	**Day 168** (± 3 days)	**-**	**175 (+3 days)**	
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**ETV**	**9**	**UNS**
Complete Physical Examination	X										
Partial Physical Examination		X	X	X	X	X	X	X	X	X	X
Height	X										
Weight	X		X	X	X	X	X	X	X		X
Waist Circumference	X							X	X		
Vital Signs	X	X	X	X	X	X	X	X	X	X	X
12-lead ECGs	X	X	X	X	X	X	X	X	X	X	
Serum Pregnancy Test	X										
Urine Pregnancy Test		X	X	X	X	X	X	X	X	X	
Laboratory Assessments[7]	X	X	X	X	X	X	X	X	X		X
Blood collection – PD study		X	X	X	X	X	X	X			
Blood collection for lymphocyte subset & Ab titer study[8]		X						X	X		
Serology (HIV, HBsAg, Anti-HBc, HCV)	X										
Adverse Event Assessment	X[9]	X	X	X	X	X	X	X	X	X	X
Efficacy Assessments[10]											
PASI, BSA, IGA	X	X	X	X	X	X	X	X	X	X	
PSSI, PP PGA, Pruritus NRS		X	X	X	X	X	X	X	X	X	
NAPSI		X			X	X		X	X	X	
Health-related Quality of Life Assessments[10]											
QIDS-SR16, DLQI, SF-12, WPAI:PSO, HEOR		X			X	X		X	X	X	
Photography											

Evaluation	Screening Period[1]	Double-Blind Titration Period (5 weeks)		Double-Blind Treatment Period					ETV and EOS Safety Follow-up Period[2]		Un-scheduled Visit[3]
	Weeks -4 to 0	Baseline visit	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Early Termin-ation Visit	Week 25 (1 Week AfterWeek 24/ETV)	
Study Day	**Day -28 to Day -1**	**Day 0**	**Day 28** (± 3 days)	**Day 56** (± 3 days)	**Day 84** (± 3 days)	**Day 112** (± 3 days)	**Day 140** (± 3 days)	**Day 168** (± 3 days)	**-**	**175 (+3 days)**	
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**ETV**	**9**	**UNS**
Photography (4 sites, 5 subjects/site)		X			X	X		X			

1. The Screening Period can only be extended on a case-by-case basis if a longer than 4 weeks' washout is required; however, the Investigator will need to obtain approval from the Medical Monitor in advance of the extension.
2. Subjects who permanently discontinue the study drug for any reason or who withdraw from the study prematurely prior to the end of the Double-Blind Treatment Period should undergo the ETV followed by the EOS Safety Follow-up Period Visit. In the event that the ETV or Week 24 Visit occurs > 1 week following the last dose of the study drug, the EOS Safety Follow-up Visit may not be required. If necessary, the Investigator may decide to extend the EOS Safety Follow-up Visits beyond 1 week to monitor recovery of safety parameters (eg, lymphopenia).
3. Table includes recommended. Unscheduled procedures, whichever are applicable, should be performed at the Investigator's discretion.
4. Initial eligibility assessment.
5. Mandatory confirmatory eligibility assessment.
6. Study drug will be dispensed as per the titration schedule described in Double-Blind Titration section.
7. Laboratory assessments include routine laboratory evaluations (i.e., chemistry, hematology, and urinalysis), and assessment of lipid panel and hsCRP
8. Blood collection for lymphocyte subset & Ab titer study can be collected at any study visit if the subject shows signs of progressive multifocal leukoencephalopathy (PML).
9. SAEs will be collected following the signing of the Informed Consent Form; AEs will be collected following the first dose of study drug.
10. Electronic device (for example: Electronic Clinical Outcome Assessments [eCOA]) will be used to record the efficacy and the health-related QoL assessments. The PSSI, PP PGA, and NAPSI will be assessed for all subjects at Baseline; if score is 0 at Baseline for any of these assessments, then the respective assessment(s) would not be required to be completed at future study visits, At baseline, the NAPSI will be evaluated for the 10 fingernails and the worst affected nail (maximum score) will be chosen as the target nail. Only the target nail will be evaluated in the subsequent visits.

Abbreviations: Ab = antibody; Anti-HBc = Hepatitis B virus core antigen; BSA = Body surface area; DLQI = Dermatological Life Quality Index; ECG = Electrocardiogram; EOS = End of Study; ETV = Early Termination Visit; HBsAg = Hepatitis B virus surface antigen; HCV = Hepatitis C virus; HEOR = Health Economics and Outcomes Research; HIV = Human immunodeficiency virus; hsCRP = High-sensitivity C reactive protein; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; PD = pharmacodynamics; PP PGA = Palmoplantar psoriasis physician's global assessment; PSSI = Psoriasis Scalp Score Index; QIDS-SR16 = Quick Inventory of Depressive Symptomatology-Self Report (16 Items); SF-12 = 12-item Short Form Survey; IGA = Investigator's Global Assessment; NRS = Numerical rating scale; WPAI:PSO = Work Productivity and Activity Impairment Questionnaire: Psoriasis

2. INTRODUCTION

The investigational product (IP) in this study is PPC-06 (tepilamide fumarate) extended release (ER) tablets, previously known as XP23829, which is a patented, oral product candidate that utilizes prodrug technology for efficient absorption into the body. Once absorbed, PPC-06 is rapidly converted to monomethyl fumarate (MMF), a fumaric acid ester (FAE) compound that has shown immunomodulatory and neuroprotective effects in cell-based systems and various preclinical models of disease. The current trial will examine the safety and efficacy of PPC-06 in the treatment of moderate-to-severe plaque-type psoriasis.

2.1 Plaque Psoriasis

Psoriasis is a chronic T-cell–mediated autoimmune disease (Ghoreschi, 2007) that affects 2% to 3% of the US population (Stern, 2004; Kurd, 2009) and 0.6% to 6.5% of the European population (Chandran, 2010). As many as an estimated 7.5 million Americans are thought to have psoriasis, making it the most common autoimmune disease in the United States (National Psoriasis Foundation). The most common phenotypic form of psoriasis, plaque psoriasis, manifests as raised, well-demarcated, red plaques with silver scales that may remit spontaneously or recur in response to environmental triggers (Nestle, 2009).

In addition to the appearance of skin plaques, there is a high degree of physical morbidity associated with psoriasis. Up to 30% of patients develop psoriatic arthritis (Zanni, 2012). Individuals with psoriasis appear to be at higher risk for a number of co-morbid conditions including obesity, myocardial infarction, cancer, diabetes mellitus, Crohn's disease and depression (Krueger, 2001; Davidovici, 2010; Mehta, 2010). Patients with severe psoriasis, on average, die five years younger than patients without psoriasis, an observation that is largely attributable to an increased risk of cardiovascular disease (Prodanovich, 2009). In addition, psoriasis can represent both a significant social and financial burden for patients. Individuals suffer from both disfigurement and social stigmatization, with an impact on mental disability comparable with that of other major medical illnesses such as heart disease and rheumatoid arthritis (Sterry, 2009). Patients with psoriasis, like those with other major medical disorders, have a reduced quality of life (QoL) and reduced levels of employment and income (Horn, 2007).

The currently available psoriasis treatments do not offer a cure. Treatment is aimed at reducing the burden of disease and achieving an improvement in its signs and symptoms (Laws, 2012). Topical agents are generally prescribed for mild and some moderate cases, while systemic agents (including biologics), and phototherapy are reserved for moderate and severe cases. Treatment decisions are based not only on the severity of the disease, but also on existing comorbidities, tolerability, side effects, and patient preferences. Several systemic agents, including methotrexate (MTX), cyclosporine, and retinoids are most commonly used (Laws, 2012). Various factors limit favorable long-term outcomes; in particular, a lack of consistent efficacy over time and the risk

of serious cumulative toxicity. Injectable biologic agents are effective for a substantial number of patients, but there is concern regarding long-term safety due to the risk of immunosuppression and the potential for development of infections, opportunistic diseases, or malignancy (Laws, 2012; Palfreeman, 2013).

2.2 Fumaric Acid Esters

Fumaric acid, an unsaturated dicarboxylic acid, is an intermediate in the citric acid cycle (Krebs cycle) and is present naturally in all cells capable of aerobic respiration. Orally administered fumaric acid is poorly absorbed and is believed to pass through the body without causing significant systemic effects. To overcome the absorption limitations of fumaric acid, simple alkyl esters of fumaric acid (FAEs), including dimethyl fumarate (DMF) and monoethyl fumarate (MEF) were synthesized and evaluated for the treatment of psoriasis in the late 1950s (Schweckendiek, 1959).

Fumaderm®, an enteric-coated oral formulation of DMF together with the calcium, magnesium and zinc salts of MEF (Fumaderm Summary of Product Characteristics [SPC] 2009) and Tecfidera®, an oral formulation of DMF without the additional MEF salts, were the first and second commercial products in the FAE class. Fumaderm was first approved in Germany for the treatment of severe psoriasis and for moderate-to-severe psoriasis vulgaris. Tecfidera is approved in the US for the treatment of relapsing forms of multiple sclerosis. In clinical trials, both Fumaderm (Ormerod, 2004; Nast, 2006; Altmeyer, 1994, 1996; Mrowietz, 1997, 1999) and Tecfidera (Langner 2005, Mrowietz 2005) demonstrated clinical efficacy in subjects with psoriasis. Both products are associated with flushing and gastrointestinal (GI) side effects such as nausea and diarrhea, and abdominal pain is also a common effect of Tecfidera. Reversible leucopenia, lymphopenia, and transient eosinophilia are frequently observed with Fumaderm; however, Tecfidera has been shown to reduce blood lymphocyte counts in multiple sclerosis patients during the first year of treatment (Tecfidera Prescribing Information, 2017).

2.3 Investigational Product

PPC-06 (tepilamide fumarate), previously known as XP23829, is a novel ester prodrug of MMF and a member of the FAE class of drugs. In a similar manner to DMF, tepilamide fumarate generates MMF during absorption and intact PPC-06 prodrug does not reach systemic circulation. MMF is the presumed active metabolite of both Tecfidera and Fumaderm. Following oral administration, PPC-06 is rapidly absorbed and hydrolyzed to release MMF and promoiety by non-specific esterases in intestinal tissues. Systemic exposure to intact PPC-06 after oral dosing in humans is negligible and the pharmacologic activity of PPC-06 is attributed to the release of the active moiety, MMF. PPC-06 is absorbed throughout the GI tract, and therefore has been successfully incorporated into an extended-release (ER) formulation, in contrast to existing immediate-release formulations of currently available FAEs (Fumaderm SPC, 2009; Tecfidera Prescribing Information, 2017).

Administration of PPC-06 reduced lymphocytes and increased eosinophils in healthy subjects. After 7 days of dosing PPC-06 (Day 8), the mean absolute reduction in blood lymphocytes from baseline ranged from -0.84 to -1.16 $\times 10^9$ /L (compared to reductions of -0.32 for DMF and -0.23 for placebo). Lymphocytes remained within normal limits (WNL) in the majority of subjects and did not drop below 0.5 $\times 10^9$ /L (or below grade 2) in any subject evaluated. These lymphocyte reductions were reversible, restoring to near baseline levels at the follow-up visit. Blood eosinophils were increased within normal limits by a mean of 0.12 to 0.20 $\times 10^9$/L from baseline for PPC-06, 0.01 for DMF, and 0.02 for placebo (see Investigator's Brochure for PPC-06 [tepilamide fumarate] Extended Release Tablets).

In 3 Phase 1 studies in healthy volunteers conducted to date, PPC-06 was generally well-tolerated and safe. The most common adverse events (AEs) of flushing and GI symptoms (nausea, diarrhea and abdominal pain) were consistent with AEs known to be associated with FAEs (see Investigator's Brochure for PPC-06 [tepilamide fumarate] Extended Release Tablets).

A Phase 2 study (XP-H-093) examined the safety and efficacy of PPC-06 400 mg QD, 800 mg QD, 400 mg twice daily (BID), and placebo in approximately 200 patients with moderate-to-severe plaque-type psoriasis. Efficacy assessments included the Psoriasis Area and Severity Index (PASI), the affected body surface area (BSA), the static Physician's Global Assessment (sPGA), the Dermatology Life Quality Index (DLQI), and the Pruritus Visual Analog Scale (VAS). The PPC-06 800 mg QD and PPC-06 400 mg BID formulations demonstrated statistically significant efficacy as defined by the primary efficacy endpoint (percent change from Baseline in total PASI score at Week 12), but did not achieve statistical significance for key secondary endpoints such as PASI-75 (at least 75% reduction in PASI score) and sPGA responder analyses, for which the study was not powered (see Investigator's Brochure for PPC- 06 [tepilamide fumarate] Extended Release Tablets). The safety profile of XP2829 was consistent with the known safety profile of the FAE medication class, particularly GI-related AEs, but some tolerability results, although limited by the short duration of the study, were potentially favorable in terms of lymphopenia and flushing (see Investigator's Brochure for PPC- 06 [tepilamide fumarate] Extended Release Tablets).

2.4 Rationale of the Study

There remains a strong unmet need for safe and convenient oral therapies that can be used long-term for the treatment of moderate-to-severe chronic plaque-type psoriasis. Despite the availability of other therapeutic options, the long-term management of psoriasis is complicated by a number of serious treatment-related limitations. Various factors limit favorable long-term outcomes, in particular, their lack of consistent efficacy over time and the risk of serious cumulative toxicity.

Based on Phase 1 studies in healthy volunteers (studies XP-H-058, XP-H-059, XP-H-076, and XP-H-116) and a Phase 2 study in moderate-to-severe plaque psoriasis patients (XP-H-093),

PPC-06 (tepilamide fumarate) ER tablets can provide not only a more sustained MMF exposure, but also may have the potential to provide an improved tolerability profile compared to other FAE prodrugs (ie, lower incidence and intensity of flushing and GI symptoms). In addition to a potential improvement in tolerability, the sustained exposure of MMF provided by PPC-06 ER tablets may also offer the convenience of a once-daily oral treatment in psoriasis. The current trial is aimed at investigating the safety and efficacy of PPC-06 in the treatment of moderate-to-severe plaque-type psoriasis.

3. TRIAL OBJECTIVES AND PURPOSE

The co-primary objectives of this study are as follows:

1. To demonstrate the efficacy of PPC-06 with respect to PASI for the treatment of moderate-to-severe plaque psoriasis, as compared with placebo at 24 weeks
2. To demonstrate the efficacy of PPC-06 with respect to IGA at 24 weeks

Secondary objectives are as follows:

1. To assess the efficacy of PPC-06 as it relates to psoriasis-related symptoms and health-related QoL measures
2. To assess the safety and tolerability of PPC-06 in subjects with moderate-to-severe plaque psoriasis
3. To evaluate the pharmacodynamics (PD) of PPC-06 through immunological analysis of peripheral blood samples.

4. STUDY DESIGN

4.1 Overall Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, multicenter study designed to assess the safety and efficacy of PPC-06 in subjects with moderate-to-severe plaque psoriasis. Study subjects will be enrolled at approximately 75 sites in the United States (US).

Approximately 400 subjects who meet the study entry criteria will be randomly assigned in a 1:1:1:1 ratio to 1 of the 4 treatment arms:

1. PPC-06 400 mg once daily (QD)
2. PPC-06 400 mg BID
3. PPC-06 600 mg BID
4. Placebo BID

The maximum study duration for each subject will be approximately 29 weeks. The study will include an up-to-4-week screening phase (which can be extended if necessary on a case-by-case

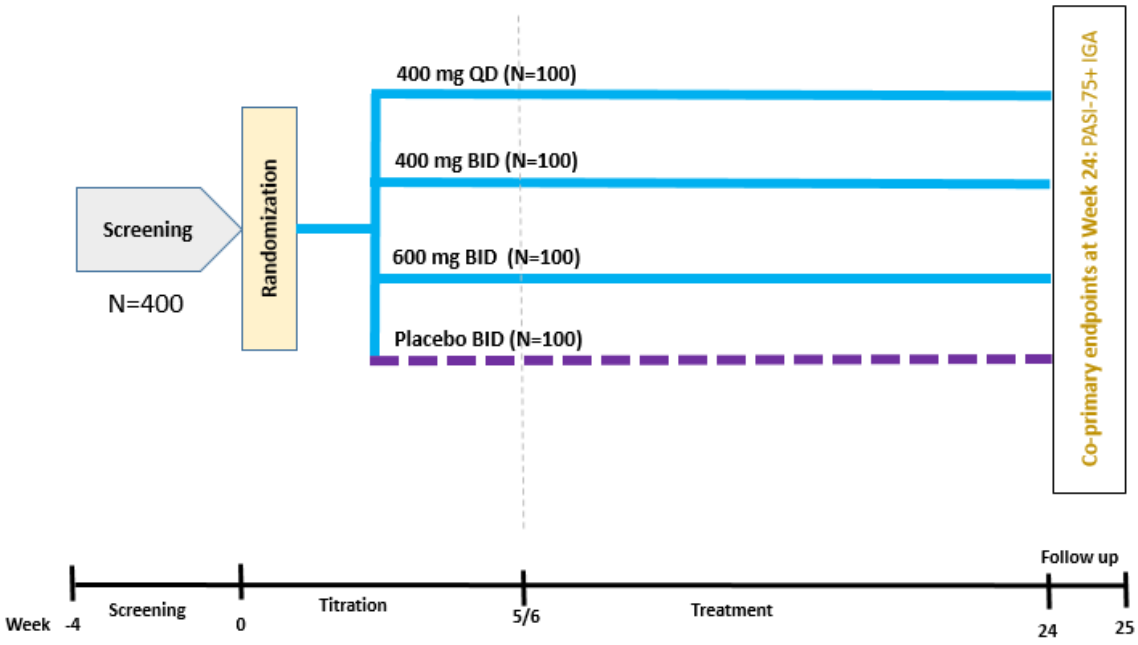
basis for washout of prohibited prior medication), a 24-week treatment phase (that includes a 5-week titration phase and a 19-week treatment period at the maintenance dose), and a 1-visit, 1-week End-of-Study (EOS) Safety Follow-up Period. If necessary, the Investigator may decide to extend the EOS beyond 1 week to monitor recovery of safety parameters (eg, lymphopenia).

Blood samples for PD assessments will be collected at baseline and at Weeks 4, 8, 12, 16, 20, and 24. PD assessments will be conducted in all subjects, with the intent of evaluating psoriasis-associated inflammatory markers. Details of PD assessment will be provided in a separate protocol.

Subjects who discontinue study drug for more than 2 consecutive weeks due to tolerability issues or for any other reason at any point during the study will not be allowed to resume treatment with study drug and will be scheduled for the early termination visit (ETV). For those subjects where the ETV occurs 1 week or more post the last study drug dose, the safety follow up visit is not required. Subjects who discontinue from the study for any other reason at any time point will directly continue to the ETV and then enter the EOS Safety Follow-up period (if required).

After having provided written informed consent, the subject will undergo screening procedures. At the end of the screening period, eligible subjects will be randomly assigned to one of the study treatment groups on Day 0 (Baseline). During the Titration/Treatment Periods, subjects will return to the study site according to the study schedule for efficacy assessments, review of study drug compliance, and assessment of concomitant medications, vital signs, AEs, and other safety parameters. At specified visits, subjects will be asked to complete questionnaires for QoL assessments. The study design is illustrated in Figure 4-1.

Figure 4-1 Study Design



4.2 Study Endpoints

4.2.1 Efficacy Endpoints

The co-primary efficacy endpoints are as follows:

- The proportion of subjects who achieve a reduction of 75% or greater from Baseline in the Psoriasis Area and Severity Index (PASI-75) at the end of Week 24
- The proportion of subjects who achieve an IGA score of clear or almost clear (IGA score 0 or 1) at the end of Week 24

Secondary efficacy endpoints include the following:

- Change from Baseline and percent change from Baseline in total PASI score at each visit in the Double-Blind Treatment Period
- The proportion of subjects who achieve PASI-50 and PASI-75 at each visit in the Double-Blind Treatment Period
- The proportion of subjects who achieve an IGA score of clear or almost clear at each visit in the Double-Blind Treatment Period
- The change from Baseline and percent change from Baseline in percent of affected BSA at each visit in the Double-Blind Treatment Period

- Mean change in the NAPSI (score range 0-8) from Baseline at Weeks 12, 16 and 24 in the target fingernail with the most severe abnormalities for those who present with lesions in fingernails at baseline
- Mean change in the PSSI score from Baseline at each visit in the Double-Blind Treatment Period for those that present with lesions on scalp at baseline
- Mean change in the Palmoplantar Psoriasis Physician's Global Assessment (PP PGA) score from Baseline at each visit in the Double-Blind Treatment Period for those that present with lesions on the palms/soles at baseline
- The change from Baseline and percent change from Baseline in pruritus NRS score at each visit in the Double-Blind Treatment Period
- Time to achieving a PASI-75 response, defined as time in days from baseline to first achieving a reduction of 75% or greater from Baseline in PASI
- Time to achieving an IGA score of clear or almost clear, defined as time in days from baseline to first achieving an IGA score of 0 or 1

4.2.2 Health Outcome/Quality of Life Endpoints

Change from Baseline in the following health outcome/QoL assessments at Weeks 12, 16, and 24:

- Quick Inventory of Depressive Symptomatology-Self Report (16 Items) (QIDS-SR16) total score
- DLQI total score
- SF-12 total score
- Work Productivity and Activity Impairment Questionnaire: Psoriasis (WPAI:PSO) score
- Health Economics and Outcome Research (HEOR) evaluation (see Section 7.3.3.5)

4.2.3 Safety Endpoints

Safety will be assessed through the monitoring of AEs, laboratory test results, vital signs, physical examinations, pregnancy testing, and 12-lead ECGs.

5. SELECTION OF STUDY POPULATION

5.1 Subject Population

Approximately 400 subjects (~100 subjects per treatment arm) will be enrolled in the study. A rationale for the choice of sample size is provided in Section 8.2 of this protocol.

Each potential subject will sign and date the most recently IRB approved informed consent document before any study-specified procedures are performed.

5.2 Inclusion Criteria

Subjects must meet all the following criteria to be eligible for participation in the study:

1. Generally healthy males or non-pregnant females age ≥18 years at the time of screening (or who have reached the state minimum legal age of consent).
2. Stable, moderate-to-severe plaque psoriasis diagnosed for at least 6 months prior to randomization (no morphology changes or significant flares of disease activity in the last 6 months in the opinion of the investigator or as reported by the subject).
3. Severity of disease meeting all 3 of the following criteria prior to randomization (at the Baseline [Day 0] visit):
   a. PASI score of ≥12
   b. Total body surface area (BSA) affected by plaque psoriasis of ≥10%
   c. IGA score of ≥3
4. Must be a candidate for phototherapy and/or systemic therapy for psoriasis.
5. Ability to independently travel to study center and to comply with all study medication and procedures or identification of a caregiver committed to assuring compliance with those study related activities.
6. Able to understand and have voluntarily signed an informed consent form (ICF) prior to undergoing any study-specific procedures.
7. Women of child-bearing potential must have had a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test (UPT) at Baseline prior to randomization.
8. Heterosexual female subjects of childbearing potential must agree to use contraception during the study which can include abstinence with an adequate secondary option should the subject become sexually active. All women of childbearing potential must complete a urine pregnancy test at the baseline visit and the test must be negative to be eligible for enrollment. (Test must have a sensitivity of at least 25 mIU/mL for human chorionic gonadotropin). A female is considered of childbearing potential unless she is a) postmenopausal for at least 12 months prior to study product administration; b) without a uterus and/or both ovaries; or has been surgically sterile (i.e., tubal ligation) for at least 6 months prior to study product administration. Reliable methods of contraception are: a) hormonal methods or intrauterine device in use ≥ 90 days prior to study product administration or barrier method plus spermicide in use at least 14 days prior to study product administration or partner has had a vasectomy at least 3 months prior to study product administration or Essure®. **Exception:** Sexually inactive female subjects of childbearing potential are not required to practice a reliable method of contraception and may be enrolled at the investigator's discretion provided that they are counseled to remain sexually inactive for the duration of the study and understand the possible risks involved in getting pregnant during the study. An abstinent heterosexual female must agree that if she becomes sexually active during the study she will use an acceptable form of contraception.
9. Willing to avoid excessive sun exposure/tanning during the study.

Note: If a subject does not meet the inclusion criteria in terms of PASI, total BSA, and/or IGA at Screening, but in the opinion of the Investigator, the subject could meet the inclusion criteria related to PASI, total BSA, and IGA at the Baseline Visit, the subject can be scheduled for the Baseline Visit where these eligibility criteria as well as all other inclusion/exclusion criteria must be met before the subject can be randomized into the study.

5.3 Exclusion Criteria

Any of the following will be regarded as a reason for exclusion from the trial:

1. Subjects with non-plaque psoriasis (ie, predominantly inverse, erythrodermic, predominantly guttate, or pustular psoriasis).
2. Subjects with drug-induced psoriasis or subjects with drug-exacerbated psoriasis that has not resolved within 4 weeks prior to screening.
3. Subjects who have received systemic non-biologic psoriasis therapy or phototherapy (including either oral and topical psoralen and ultraviolet A (PUVA) light therapy, ultraviolet B, or self-treatment with tanning beds or therapeutic sunbathing) within 4 weeks prior to the Baseline Visit.

   Subjects who had topical psoriasis treatment within the previous 2 weeks prior to the Baseline Visit.

   Exceptions: Mild/least potent topical steroids will be permitted for use limited to the face, axilla, and/or genitalia. Medicated shampoos containing the active ingredients zinc pyrithione, salicylic acid, selenium sulfide, or ketoconazole will be permitted for use in the shower on the scalp only
4. Subjects with history of concurrent or recent use of any biologic agent within the following washout periods prior to baseline visit:
   - Etanercept – 35 days
   - Infliximab, adalimumab - 12 weeks
   - Ustekinumab – 24 weeks
   - Any other biologic agent <5 half-lives prior to the Baseline Visit

   Note 1: Screening visit can be extended on case-by-case basis (but no more than additional 4 weeks) to complete the wash out.

   Note 2: A maximum of 30% of subjects with prior biologic use (ie, subjects who received systemic biologic drugs in the past) will be enrolled, but they must be washed out prior to randomization.
5. Subjects with prior exposure to natalizumab, rituximab, or belilumab in the past 1 year prior to screening visit.
6. Subjects with history of use of any investigational drug within 28 days prior to randomization, or 5 pharmacokinetic/ pharmacodynamic half-lives (whichever is longer).
7. Subjects who have failed to improve on 3 or more systemic therapies.
8. Subjects who cannot avoid excessive sun exposure or use of tanning booths for at least 4 weeks prior to the Baseline Visit and during the day for the entire duration of the study.

9. Subjects with unstable or significant illness, including the presence of laboratory abnormalities or electrocardiogram (ECG) abnormalities, at Screening that, in the opinion of the Investigator, would place the subject at unacceptable risk if he/she were to participate in the study (eg, clinically significant abnormality on ECG, any other auto-immune conditions where subject is on immunosuppressive agents).
10. Subjects with sarcoidosis, active tuberculosis, or incompletely treated tuberculosis (TB), or any other serious systemic infection.
11. Any skin condition (eg, eczema) that would confound the ability to interpret data from the study.
12. Subjects whose BMI is >39.
13. Subjects with a present or past history of any neurological conditions such as stroke, transient ischemic attack, seizures, cranial nerve palsies, major head trauma, brain tumor, demyelinating disorders.
14. Subjects with a current history of any medical condition associated with significant gastrointestinal (GI) events such as nausea, vomiting, constipation, abdominal pain, or diarrhea, which in the opinion of the investigator would affect the tolerability of the drug.
15. Subjects with severe gastritis, duodenal ulcer, severe symptomatic lactose intolerance, irritable bowel syndrome, present or a past history of inflammatory bowel disease or severe dysphagia.
16. Subjects with a persistent history (more than 3 consecutive months) of lymphopenia (below the lower limit of normal [LLN]) in the last 2 years.
17. Subjects who had prior treatment with dimethyl fumarate (Fumaderm® or Tecfidera®) or any other fumaric acid ester (FAE) containing products.
18. Subjects who at Screening and/or randomization have uncontrolled high blood pressure values, which, in the opinion of the Investigator, may increase the risk of cardiovascular events.
19. Subjects who at Screening have creatinine clearance <60 mL/min.
20. Subjects who, according to the Reference Laboratory Manual, at Screening have:
    a. White blood cells (WBC) < 3000/mm³
    b. Neutrophils/granulocytes less than the LLN
    c. Platelets <110,000/ mm³
    d. Lymphocytes <1000/mm³
    e. Serum creatinine >1.5× the upper limit of normal (ULN)
    f. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2×ULN
    g. Significant proteinuria measured as 3+ or above in urine dipstick in two samples taken on two different days
    h. Non-fasted blood glucose > 200 mg/dL

    Note: Laboratory tests that cross these thresholds can be repeated once if the Investigator has a clinical reason to believe that a result may be erroneous in which case the laboratory result should be discussed and agreed with the Medical Monitor before repeating it. The repeat value can be accepted if it meets protocol criterion.

Subjects who have chronically abnormal laboratory values beyond any of the above exclusionary thresholds are excluded even if they are deemed clinically normal.

21. Subjects who have positive results at Screening for hepatitis B (HBsAg and anti-HBc), hepatitis C, or human immunodeficiency virus (HIV).
22. Subjects who have a known immunodeficiency, receive immune modulatory/immune suppressant therapy, or are immunocompromised.
23. Subjects with malignancy (except for adequately treated basal cell carcinoma, squamous cell carcinoma, and carcinoma in situ of the cervix) or subjects with history of malignancy, with evidence of recurrence within the previous 5 years.
24. Subjects with a history of drug or alcohol use disorder based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria (within the 6 months prior to screening) as reported by the subject or known to the Investigator.
25. Subjects with cognitive deficit or psychiatric syndrome of any etiology that may influence compliance with study procedures or study outcome.
26. Subjects with a history of allergy to any component of the study drug.
27. Women who are lactating or breastfeeding.
28. Investigator site personnel directly affiliated with this study and/or their immediate families.
29. Sponsor employees or its designee or employees of third-party organizations involved in the study.
30. Prisoners or subjects who are involuntarily incarcerated.

5.4 Discontinuation of Treatment or Assessments

Subjects can be removed from the study for any of the following reasons:

- AE(s)
- Protocol violation
- Withdrawal by subject (subject voluntarily discontinued study participation)
- Lost to follow-up
- Pregnancy
- Study terminated by sponsor
- Investigator decision
- Non-compliance with study drug (<80% or >120%)
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Unblinding of a subject for any reason

All subjects meeting the above withdrawal criteria are to be evaluated at the safety follow-up EOS visits unless they have withdrawn full consent. The reason for a subject's permanent withdrawal is to be recorded on the appropriate electronic case report form (eCRF). Subjects

who prematurely withdraw from the study for AEs are to be monitored for up to 30 days after the subject stopped study treatment or until the abnormal parameter resolves or stabilizes. Pregnancies are to be reported to the sponsor or designee within 24 hours of learning of its occurrence, and the pregnancy is to be monitored to determine outcome. Investigators are to document their attempts to contact subjects who are lost to follow-up.

As a class, FAEs are known to have an effect on lymphocyte and eosinophil counts and can have hepatotoxic and nephrotoxic effects at excessive exposures. The following study drug discontinuation criteria are to be implemented to reduce the risk of toxicity for individual subjects and to investigate the time course of recovery of affected safety parameters.

If any of the following criteria are met, study treatment will be permanently discontinued and the subject will be scheduled for an ETV followed by the Safety Follow-up Visit.

- Lymphocytes <500/mm^3 at any visit
- Lymphocytes <800/mm^3 on 3 consecutive visits
- ALT or AST >8×ULN on repeat examination (if assumed increase is related to study drug)
- ALT or AST >5×ULN for more than 2 weeks on repeat examination (if assumed increase is related to study drug)
- ALT or AST >3×ULN and either total bilirubin >2 × the ULN or International Normalized Ratio (INR) >1.5 on repeat examination (if assumed increase is related to study drug) in presence of normal alk phosphate.
- ALT or AST >3×ULN with concurrent appearance or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (>5% eosinophils on differential leukocyte count
- Serum creatinine >1.5×ULN on repeat exam (if assumed increase is related to study drug)
- Proteinuria measured as 3+ or above in urine dipstick on 2 consecutive samples, 4 weeks apart
- If advised by the Medical Monitor or PML experts.

Laboratory tests can be repeated earlier than the next scheduled consecutive visit at the investigator's discretion and any associated safety issue should be followed up as per the Investigator's clinical judgment until resolution/stabilization.

Replacement Policy

Subjects who prematurely discontinue from the study after randomization will not be replaced.

5.5 Dietary and Lifestyle Restrictions

Subjects must avoid phototherapy, excessive or prolonged sun exposure, or use of ultraviolet (UV) light sources within 28 days of randomization and throughout the study. Subjects will not otherwise alter their lifestyle and will not alter their diet during the study except to remain compliant with the inclusion and exclusion criteria.

6. STUDY TREATMENTS

6.1 Investigational Products and Controls

The study product under investigation in this study, PPC-06 (tepilamide fumarate) is a prodrug of MMF and a member of the FAE class of compounds. It will be administered as an extended release (ER) tablet formulation for oral administration via blister wallets during the Double-Blind Titration Period and via bottles during the Double-Blind Treatment Period. Three dosages of PPC-06 ER tablets (400 mg QD, 400 mg BID, and 600 mg BID) and a placebo BID regimen (using placebo tablets identical in appearance to the active-treatment tablets) will be studied.

PPC-06 ER tablets are white round tablets of 100 mg and 200 mg dose strength, and are manufactured and packaged under Good Manufacturing Practice (GMP) regulations. Tablets are formulated with PPC-06 and the following excipients: lactose, hypromellose, colloidal silicon dioxide, hydroxypropyl cellulose, and magnesium stearate.

The placebo tablets will contain the same ingredients as the active formulation(s) without the active ingredient, and will be identical in appearance to the active PPC-06 ER tablets. Depending on the dose group, subjects are expected to ingest 2.98g to 2.31g of lactose daily from study medication, which is approximately the amount of lactose in ¼ cup of whole milk.

6.2 Dosing Regimen

Dosages and pill allocations for the Titration Period (Weeks 1-5) and for the Treatment Period (Weeks 6-24) are shown in Table 6-1 and Table 6-3, respectively. The dosing regimen for the Titration Period is presented in Table 6-2. Note: Doses specified in red followed by a 'P' indicate Placebo.

Double-Blind Titration Period (Baseline through Week 5)

Following completion of the pre-randomization Screening Period, eligible subjects will be randomized in a 1:1:1:1 ratio to 1 of the 4 treatment arms and will enter the 5-week Double-Blind Titration Period. The first dose of study drug will be taken the day after the Baseline Visit (on Day 1). If a subject misses a dose (or several doses) during the Titration Period, they should skip that dose and continue with the next scheduled dose. At least 4 hours should elapse between doses, but ideally 8-12 hour intervals should be maintained. If a subject misses 7 or more consecutive days of dosing during the Titration Period, the site should contact the Sponsor or designee for guidance on how to proceed. At Visit 3 (Week 4), the subjects will

be instructed to continue 1 more week of Titration dose (Week 5 of blister wallets) and will also be given a kit of bottles which will allow dosing until Visit 4. Please refer to Table 6-1 for titration schedule.

Double-Blind Treatment Period (Week 6 through Week 24)

Subjects will receive PPC-06 400 mg QD, PPC-06 400 mg BID, PPC-06 600 mg BID, or Placebo BID from Week 6 through Week 24, based on the treatment arm to which they were randomized. Subjects will return to the clinic every 4 weeks (±3 days) thereafter for drug accountability and to undergo safety and efficacy evaluations per the schedule of assessments (Table 1-1).

- Visit 4: End of Week 8
- Visit 5: End of Week 12
- Visit 6: End of Week 16
- Visit 7: End of Week 20
- Visit 8: End of Week 24
- Visit 9: End of Week 25

Table 6-1 Treatment Schedule - Titration Period (Weeks 1-5)

	400 mg QD	400 mg BID	600 mg BID	Placebo BID
Week 1 (Days 1-7)	100 P (am) + 100 P (am) 100 P (pm) + 100 (pm)	100 P (am) + 100 P (am) 100 P (pm) + 100 (pm)	100 (am) + 100 P (am) 100 P (pm) + 100 (pm)	100 P (am) + 100 P (am) 100 P (pm) + 100 P (pm)
Week 2 (Days 8-14)	200 P (am) + 200 P (am) 200 P (pm) + 200 (pm)	200 P (am) + 200 P (am) 200 P (pm) + 200 (pm)	200 (am) + 200 P (am) 200 P (pm) + 200 (pm)	200 P (am) + 200 P (am) 200 P (pm) + 200 P (pm)
Week 3 (Days 15-21)	100 P (am) + 100 P (am) 200 (pm) + 200 (pm)	100 P (am) + 100 (am) 200 P (pm) + 200 (pm)	100 (am) + 100 (am) 200 (pm) + 200 (pm)	100 P (am) + 100 P (am) 200 P (pm) + 200 P (pm)
Week 4 (Days 22-28)	200 P (am) + 200 P (am) 200 (pm) + 200 (pm)	200 P (am) + 200 (am) 200 P (pm) + 200 (pm)	200 (am) + 200 (am) 200 (pm) + 200 (pm)	200 P (am) + 200 P (am) 200 P (pm) + 200 P (pm)
Week 5 (Days 29-35)	200 P (am) + 200 P (am) 200 (pm) + 200 (pm) + 200 P (pm)	200 P (am) + 200 (am) 200 (pm) + 200 (pm) + 200 P (pm)	200 (am) + 200 (am) 200 (pm) + 200 (pm) + 200 (pm)	200 P (am) + 200 P (am) 200 P (pm) + 200 P (pm) + 200 P (pm)

Table 6-2 Titration Regimen

Visit	Weeks (Days)	Tablet regimen for all groups
Baseline*	Week 1 (Days 1-7)	Take 2 tabs in the morning and 2 tabs in the evening from the blister
	Week 2 (Days 8-14)	Take 2 tabs in the morning and 2 tabs in the evening from the blister
	Week 3 (Days 15-21)	Take 2 tabs in the morning and 2 tabs in the evening from the blister
	Week 4 (Days 22-28)	Take 2 tabs in the morning and 2 tabs in the evening from the blister
	Week 5 (Days 29-35)	Take 2 tabs in the morning and 3 tabs in the evening from the blister
Week 4# (Day 28)	Week 6 (Days 36-42) to Week 8 (Days 50-56)	Take 1 tab from AM Bottle 1 and 2 tabs from AM Bottle 2; repeat the process in the night with PM bottles.

* = Subjects will be given 5 blister wallets (for Weeks 1-5)
# = Subjects will be given 2 sets of 2 Bottles as mentioned.

Table 6-3 Treatment Schedule: Treatment Period (Weeks 6-24)

Visit	PPC-06 400 mg QD Regimen	PPC-06 400 mg BID Regimen	PPC-06 600 BID Regimen	PPC-06 Placebo BID Regimen
	Week 6 – Week 24	Week 6 – Week 24	Week 6 – Week 24	Week 6 – Week 24
Weeks 8-20 (Dispense 2 sets of 2 Bottles)[1]	200 P (am) + 200 P (am) + 200 P (am) 200 (pm) + 200 (pm) + 200 P (pm)	200 P (am) + 200 (am) + 200 (am) 200 (pm) + 200 (pm) + 200 P (pm)	200 (am) + 200 (am) + 200 (am) 200 (pm) + 200 (pm) + 200 (pm)	200 P (am) + 200 P (am) + 200 P (am) 200 P (pm) + 200 P (pm) + 200 P (pm)

[1] Subjects will be given 2 sets of 2 bottles (2 morning (AM) bottles + 2 evening (PM) bottles)
AM Bottles: AM Bottle 1 (30 count) and AM Bottle 2 (60 count)
PM Bottles: PM Bottle 1 (30 count) and PM Bottle 2 (60 count)
Take 1 tablet from (AM) Bottle 1 and 2 tablets from (AM) Bottle 2; repeat the process in the evening with (PM) bottles

6.3 Dose Modification

At any point during the Double-Blind Titration or Treatment Periods, a temporary dose reduction or interruption may be considered in circumstances where a subject has a tolerability issue such as flushing or GI intolerance. The Investigator may use other medications such as loperamide for diarrhea (or local standard of care) for tolerability management as long as the medication is not one of the prohibited/restricted medications.

During the Double-Blind Treatment Period (Weeks 6-24), in the event of a temporary dose reduction (no more than 2 weeks), 1 tablet from each Bottle 2 (AM and PM) will be reduced. When the tolerability issues resolve, study drug should be titrated back up to the respective treatment dose. If the tolerability issues return at the higher dose, subjects may be discontinued from the study.

Note: Subjects who discontinue study treatment for more than 2 weeks during the Double-Blind Titration or Treatment Periods due to tolerability issues or for any other reason at any point during the study will not be allowed to resume their study treatment and will be scheduled for an ETV. Subjects who discontinue from the study for any reason at any time point will directly continue to the ETV.

6.4 Packaging and Labeling

The IP will be labeled according to all applicable federal regulations and be printed in the local language.

The study medication will be supplied to the clinical site(s) in kits containing 5 weeks of blister wallets which will be used for the Titration Period, as well as kits containing 2 sets of 2 Bottles which will be used for the Treatment Period. The blister wallet kits will contain a total of 147 tablets, and the Bottle kits will contain 2 AM and 2 PM bottles:

- AM Bottle 1 – 30 tablets
- AM Bottle 2 – 60 tablets
- PM Bottle 1 – 30 tablets
- PM Bottle 2 – 60 tablets

6.5 Storage

Investigational product must be stored at controlled room temperature (20-25°C, 68-77°F) with excursions permitted to 15°-30°C (59°-86°F). Subjects will be advised to keep study medication out of reach of children and persons who may not be able to read or understand the label. All study medication should be kept in a secure area inaccessible to unauthorized individuals.

All remaining IP will be returned to the sponsor or its designee after final drug accountability has been completed.

6.6 Assignment to Treatment

6.6.1 Randomization

All subjects who enter into the screening period for the study (defined as the point at which the subject signs the ICF) will receive a subject identification number through the Interactive Web Response System (IWRS). This number (which will consist of the site number followed by the subject number) will be used to identify the subject throughout the study and must be used on all study documentation related to that subject. The subject identification number must remain constant throughout the entire study; it must not be changed at the time of screening or randomization. This number will not be the same as the assigned randomization number. The IWRS will be used for randomization. A subject can be rescreened on a case by case basis with input from the Medical Monitor. In the event a subject is rescreened, the subject will be (re)presented with the ICF and a new subject identification number will be given by IWRS.

Once assigned to a subject, a subject identification number will not be reused. If the subject fails to be randomized for any reason, the reason for not being randomized will be entered in the subject's eCRF.

The randomization scheme will be reviewed and approved by a member of the sponsor's Biostatistics and Data Management (BDM) group or designee. The sites will randomize eligible subjects by contacting IWRS at Visit 2 after all of the relevant Baseline procedures are completed and assessed as appropriate. A subject who fulfills the study eligibility requirements will be randomly assigned to treatment. The randomization will be stratified by prior biologic use.

The IWRS will assign a randomization number to the subject, which will be used to link the subject to the treatment group and will specify a unique Blister Wallet IP kit number for the IP to be dispensed to the subject at Visit 2 for the Titration Period. The sites will log in to IWRS during each subsequent subject visit to obtain the kit numbers of the Bottle Kits to be dispensed at study Visits 3-7.

6.6.2 Blinding

This is a double-blind study. The investigator, study coordinator(s), subjects and the Sponsor study team and its representatives, will be blinded to the identity of the randomized treatment assignment from the time of randomization until database lock. Randomization data will be kept in strict confidence by the statistician who generated the randomization schedule, the IWRS provider, and the vendor involved in the IP labeling. All active and placebo IP will be of identical appearance, regardless of the dose. Study materials will be packaged and issued in a manner designed to maintain the blind.

Unblinding by study site personnel for AEs should only be performed in an emergency, when knowledge of the subject's treatment assignment is essential for the clinical management or welfare of the subject (Section 13.1, Emergency Unblinding).

Prior to unblinding, the investigator should make every effort to first contact the Medical Monitor (or designee) and should assess the relationship of an AE to the administration of the IP. The investigator must then log in to the IWRS to unblind the individual subject's treatment assignment. If the blind is broken for any reason, the investigator must record the date and reason for breaking the blind on the appropriate eCRF and source documents.

For details of the procedure for unblinding of individual subjects in cases of emergency see Section 13.1.

6.7 Prior and Concomitant Therapy

All medications, including over-the-counter (OTC) drugs, taken within 30 days prior to the start of the study (Screening Visit) will be recorded at Screening. Thereafter, a record of all medications and supportive therapy taken during the course of the study will be made. Information regarding the total daily dose, route of administration, start and discontinuation dates, and indication are to be recorded on the subject's eCRF.

Changes to medications, including prescription, OTC, herbal preparations, or mineral supplements taken for treatment of psoriasis will not be allowed without prior approval of the Medical Monitor or designee. Use of hormonal contraceptives is to be stabilized for at least 3 months prior to randomization.

The use of non-medicated emollients is permitted during the study; every effort is to be made to maintain the same regimen following Screening and throughout the study. The use of color-cosmetics and sunscreens/sunblocking agents is allowed; however, excessive and/or prolonged exposure to direct sun must be avoided during the trial.

The use of non-steroidal anti-inflammatory drugs (NSAIDs) or analgesic treatments will be permitted to treat symptoms of psoriatic arthritis on a PRN basis.

Restrictions regarding prior and concomitant therapies, as listed in the Exclusion Criteria, must be observed during the study, including the treatment and follow-up periods. Dose adjustments of any permitted concomitant medications should be avoided during the study, if possible.

The following therapies are prohibited from use at any time during the study:

- Any drug known to influence the course of psoriasis such as lithium, beta-blockers, and antimalarial therapies
    - Stable doses of beta-blockers are permitted if there is no history of exacerbation of psoriasis due to beta-blockers and the dose will be kept unchanged throughout the trial.

- Any live vaccines, except flu vaccines.
- Any systemic non-biologic immunosuppressive medication (eg, MTX, cyclosporine, mycophenylate mofetil, 6-thioguanine)
- Biologic agents (eg, etanercept, alefecept) and any antibody (eg, infliximab, adalimumab, golimumab, ustekinumab)
- Any systemic steroid (steroid inhalers, nasal sprays and eye drops or intra-articular injections are permitted)
- Phototherapy
- Laser therapy for psoriasis or other skin conditions
- Topical corticosteroids (other than the limited use of mild topical steroids specified below under "Rescue Medication"), vitamin D analogs, tar preparations, salicylic acid, or urea preparations
- Topical or systemic calcineurin inhibitors (eg, tacrolimus, pimecrolimus)
- Topical or systemic retinoids (eg, tazarotene, tretinoin, adapalene)
- Topical (ointment and/or baths) or oral fumaric acid derivatives
- Cytostatic drugs (eg, cyclophosphamide, ifosfamide, vinblastine, vincristine, procarbazine, dacarbazine, 6-mercaptopurine, 5-fluorouracil, adriamycin)
- Any investigational drug or therapy, or approved drug or therapy for investigational use

Rescue and Concomitant Medication

The use of rescue medications for the treatment of psoriasis may be permitted during the Double-Blind Titration and/or Treatment Period at the investigator's discretion. Subjects will be considered a treatment failure if rescue therapy is required; however, they can continue for safety monitoring, if required. Concomitant medications permitted for use for psoriasis are restricted to bland emollients and other non-medicated interventions. This excludes any topical agents that contain pharmacologically active ingredients (eg, salicylic acid, alpha-hydroxy acids, urea, etc.). Dose adjustments of any permitted concomitant medications should be avoided during the study, if possible.

Note: Limited use of mild topical steroids (Class VI or VII in North America) for the treatment of psoriasis on limited areas (face, axilla, and/or genitalia) is permitted. Subjects will be permitted to use medicated shampoos (on the scalp only in the shower). This will not be considered as rescue medication.

6.8 Treatment Compliance

Subject compliance with study drug will be assessed by the investigator and/or study personnel at each visit using direct questioning, and pill counts. Deviations from the prescribed treatment regimen will be recorded on the source document and the subjects' eCRFs. All returned blister wallets or bottles must be reviewed at every visit while the subject is still at the clinic to

determine if the subject is dosing as instructed. Deviations from the prescribed treatment regimen will be recorded on the source document and the subjects' eCRFs.

During the Titration Period, if a subject misses a dose (or several doses), they should skip that dose and continue with the next scheduled dose. If a subject misses 7 or more consecutive days of dosing during the Titration Period, the site should contact the Sponsor or designee for guidance on how to proceed.

During the Double-Blind Treatment Period, a subject is said to be compliant if they have taken 80% to 120% of the expected tablets of study medication. If a subject has taken less than 80% or more than 120% of the expected tablets since the last visit, the subject should be counseled. In cases where noncompliance is continual, the site should contact the study Medical Monitor or designee to discuss other options, such as withdrawing the subject.

Compliance calculation has been defined in Section 8.5.

7. VISIT SCHEDULE AND ASSESSMENTS

7.1 Study Procedures

The visit schedule and assessments are summarized in Table 1-1.

7.2 Study Visits and Assessments

7.2.1 Visit 1 Screening (Day -28 to Day -1)

Screening of subjects will start at Visit 1 and continue up to 4 weeks prior to Baseline/ Randomization (Visit 2) unless an extension is granted by the Medical Monitor in advance of the Visit 2. Screening procedures will include:

- Review study information with subject and obtain written informed consent
- Register subject in IWRS to receive Screening Number
- Review inclusion and exclusion criteria with the subject to determine the subject's eligibility
- Perform psoriasis assessments to ensure that subject will meet PASI, IGA, and BSA requirements at Baseline visit
- Collect medical history and demographic information
- Collect psoriasis medical history and use of all prior medications and non-drug therapies to treat psoriasis
- Review and record prior medications (used within the previous 30 days) and concomitant medications (medications currently used)
- Perform a complete physical examination, including height, weight, and waist circumference

- Measure vital signs (systolic and diastolic blood pressure, heart rate, and respiratory rate) with subject in a seated position
- Obtain a 12-lead ECG
- Obtain blood and urine samples for routine laboratory profile evaluations including hematology, serum chemistry, and urinalysis
- Obtain samples for serology: human immunodeficiency virus (HIV), hepatitis B virus surface antigen (HBsAg), antibodies to hepatitis B core antigen (anti-HBc), and hepatitis C virus (HCV)
- Obtain a sample for a serum pregnancy test for all female subjects. Instruct all female subjects to use approved form(s) of contraception
- Record any SAEs (from time of signing ICF)
- If subject meets the inclusion/exclusion criteria, instruct the subject to begin washout of prohibited medications and schedule Visit 2 pending receipt of lab and ECG results

7.2.2 Visit 2 – Randomization/Baseline (Day 0)

- Perform psoriasis assessments:
  - PASI, BSA, IGA
  - NAPSI for fingernails, PSSI, PP PGA for all subjects; if score is 0 at Baseline for any of these assessments, then the respective assessment(s) would not be required to be completed at future study visits
- Confirm psoriasis medical history and previous psoriasis therapies
- Confirm medical history and record any new findings
- Review and record medication changes since the Screening visit, including changes in prescription and OTC medications, herbal preparations, and vitamin and/or mineral supplements and non-drug therapies
- Confirm washout of prohibited medications
- Perform a partial physical examination with focus on previously noted abnormalities in organ systems, including skin
- Measure vital signs (systolic and diastolic blood pressure, heart rate, and respiratory rate) with subject in a seated position
- Obtain a 12-lead ECG (Baseline Visit central ECG reading will not be available prior to Randomization; Investigator must review Baseline ECG tracing to confirm eligibility prior to Randomization. Subject with clinically significant ECG findings in the Investigator's opinion will be screen failed. Investigator also must review the central ECG reading when results are available. Subjects with unacceptable ECG findings will be discontinued from the study)
- Review inclusion and exclusion criteria to confirm that the subject is qualified for study participation

- Perform a urine pregnancy test for female subjects of childbearing potential. Instruct all female subjects to use approved form(s) of contraception
- Obtain blood and urine samples for routine laboratory profile evaluations including hematology, serum chemistry, and urinalysis
- Blood collection for PD study as well as lymphocyte & Ab titer study
- Record any SAEs
- Have the subject complete the following assessments:
  - Pruritus NRS, DLQI, SF-12, QIDS-SR16, WPAI: PSO, HEOR
- Perform photography (at selected 3 sites only); see photography reference materials for details
- Randomize the subject in IWRS after confirmation of eligibility criteria
- Instruct subjects on dosing and dispense study drug
- Dispense educational materials for AE management (provided by Sponsor)
- Provide subject with Bristol Stool Chart; have the subject confirm the average frequency of their bowel movements for the past 15 days and the general consistency of the stool using the Bristol Stool Chart

7.2.3 Visit 3 (Week 4), Visit 4 (Week 8), Visit 5 (Week 12), Visit 6 (Week 16), Visit 7 (Week 20), and Visit 8 (Week 24)

- Review any concomitant medication changes since the previous study visit
- Perform a partial physical examination with focus on previously noted abnormalities in organ systems, including skin
- Measure weight
- Measure waist circumference (Week 24 only)
- Measure vital signs (systolic and diastolic blood pressure, heart rate, and respiratory rate) with subject in a seated position
- Record a 12-lead ECG
- Obtain blood and urine samples for routine laboratory profile evaluations including hematology, clinical chemistry, and urinalysis
- Blood collection for PD study
- Blood collection for lymphocyte subset & Ab titer study (Week 24, or at any time during the study if subject shows signs of PML)
- Perform a UPT for females of childbearing potential. Ensure that female subjects of childbearing potential are using approved method(s) of contraception.
- Record any AEs

- Perform psoriasis assessments if applicable:
  - PASI, BSA, IGA
  - NAPSI for target fingernail, if applicable (weeks 12, 16 and 24 only)
  - PSSI, PP PGA (if applicable)
- Have the subject perform the following assessments:
  - Pruritus NRS
  - DLQI, SF-12, QIDS-SR16, WPAI: PSO, HEOR (Weeks 12, 16, and 24 only)
- Perform photography (at selected 3 sites only) (Weeks 12, 16, and 24 only); see photography reference materials for details
- Assess IP compliance/accountability
- Dispense IP as applicable (Weeks 4, 8, 12, 16, and 20)

7.2.4 Early Termination Visit

- Review any concomitant medication changes since the previous study visit
- Assess IP compliance/accountability
- Perform a partial physical examination with focus on previously noted abnormalities in organ systems, including skin
- Measure weight
- Measure waist circumference
- Measure vital signs (systolic and diastolic blood pressure, heart rate, and respiratory rate) with subject in a seated position
- Record a 12-lead ECG
- Perform a UPT for females of childbearing potential. Ensure that female subjects of childbearing potential are using approved method(s) of contraception.
- Obtain blood and urine samples for routine laboratory profile evaluations including hematology, clinical chemistry, and urinalysis
- Blood collection for lymphocyte subset & Ab titer study
- Record any AEs
- Perform psoriasis assessments:
  - PASI, BSA, IGA
  - NAPSI for target fingernail, PSSI, PP PGA (if applicable)
- Have the subject perform the following assessments:
  - Pruritus NRS

- DLQI, SF-12, QIDS-SR16, WPAI: PSO, HEOR

7.2.5 Safety Follow-up Visit (Week 25 [+3 days], or 1 Week [+3 days] after ETV, unless final dose was taken >7 days prior to Week 24/ETV)

- Review any concomitant medications used since the previous study visit
- Perform a partial physical examination with focus on previously noted abnormalities in organ systems, including skin
- Measure vital signs (systolic and diastolic blood pressure, heart rate, and respiratory rate) with subject in a seated position
- Record a 12-lead ECG
- Perform a UPT for females of childbearing potential. Ensure that female subjects of childbearing potential are using approved method(s) of contraception.
- Record any AEs
- Perform psoriasis assessments:
  - PASI, BSA, IGA
  - NAPSI for the target fingernail , PSSI, PP PGA (if applicable)
- Have the subject perform the following assessments:
  - Pruritus NRS
  - DLQI, SF-12, QIDS-SR16, WPAI: PSO, HEOR

7.2.6 Unscheduled Visit

If a subject returns to the site for an unscheduled visit, the following assessments may be performed at the discretion of the Investigator:

- Review any concomitant medications used since the previous study visit
- Perform a partial physical examination with focus on previously noted abnormalities in organ systems, including skin
- Measure weight
- Measure vital signs (systolic and diastolic blood pressure, heart rate, and respiratory rate) with subject in a seated position
- Obtain blood and urine samples for routine laboratory profile evaluations including hematology, clinical chemistry, and urinalysis
- Record any AEs

7.3 Efficacy Assessments

Efficacy will be evaluated via psoriasis assessments and measures of QoL.

Psoriasis assessments include the PASI, the affected BSA, and the IGA. Subject-reported assessments of health-related QoL include the DLQI, 12-Item Short Form Survey (SF-12), the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR), the WPAI:PSO, the HEOR, and the Pruritus NRS.

Other psoriasis assessments to be performed as applicable include the NAPSI for the target fingernail, the PSSI score, and the PP PGA score.

Brief descriptions of these assessments are presented as follows.

7.3.1 Co-Primary Efficacy Assessments: Psoriasis Area and Severity Index and Investigator's Global Assessment

The investigator or designee will assess the extent and severity of the subjects' psoriasis using the PASI scoring system and will perform a global assessment of disease severity using the IGA. The PASI scale is provided in Appendix 1; the IGA is a 5-point scale which measures the investigator's or designee's impression of the disease at a single point. Assessments will be performed at the visits specified in Table 1-1. Sites should make every effort to ensure consistency in evaluators across visits, especially between Baseline and Week 24.

Psoriasis Area and Severity Index

The PASI is a measure of the average redness, thickness, and scaliness of the lesions (each graded on a 0–4 scale) and weighted by the area of involvement (Fredriksson, 1978). There are a few validation studies performed describing, with some limitations, the construct validity, face validity, and sensitivity to change (Ashcroft, 1999). National Psoriasis Foundation Medical Advisory Board standardized the definitions of events of psoriasis recurrence based on PASI, including the definition of relapse, which is a loss of at least 50% of PASI improvement after discontinuation of treatment in patients who had achieved a clinically meaningful response; and rebound, which is PASI ≥125% of Baseline or new generalized pustular, erythrodermic, or more inflammatory psoriasis (Carey, 2006; Gordon, 2005). In the current trial, PASI improvement will be evaluated from Baseline to all visits during the Titration and Treatment Periods, and clinically meaningful response is defined as PASI-50 (Carlin, 2004).

Investigator's Global Assessment

The IGA should be performed by the same evaluator (rater) who performs the PASI assessments and all efficacy assessments should be performed by the same evaluator throughout the study when possible. The scale in Table 7-1 will be used for the IGA assessment:

Table 7-1 Investigator's Global Assessment (IGA)

Score	Grade	Definition
0	Clear	No signs of psoriasis Post-inflammatory hyperpigmentation may be present
1	Almost clear	No thickening to minimal plaque elevation Normal to slight pink coloration/faint erythema Focal to minimal scaling
2	Mild	Slight elevation/thickening Pink to light red coloration Predominantly fine scaling partially or mostly covering lesions
3	Moderate	Clearly distinguishable/distinct thickening Definite red coloration Coarse scaling covering most plaques
4	Severe	Marked thickening with hard/sharp edges Bright to deep dark red coloration Thick/coarse scaling covering almost all or all lesions

Adapted from: Langley RGB, Feldman SR, Nyirady J, van de Kerkhof P, et al. The 5-point Investigator's Global Assessment (IGA) Scale: A modified tool for evaluating plaque psoriasis severity in clinical trials. J Dermatolog Treat. 2015;26(1): 23-31.

7.3.2 Secondary Efficacy Assessments

Secondary efficacy assessments will be performed at the visits specified in Table 1-1.

7.3.2.1 Affected Body Surface Area

BSA will be calculated using handprint methodology, comparing the size of the affected area to the size of the subject's entire handprint, which equates to approximately 1% BSA. Evaluators should use the method consistently throughout the trial.

7.3.2.2 Nail Psoriasis Severity Index

The NAPSI is a numeric, reproducible, objective, simple tool for evaluation of nail psoriasis. This scale is used to evaluate the severity of nail bed psoriasis and nail matrix psoriasis by area of involvement in the nail unit. The NAPSI is provided in Appendix 2.

7.3.2.3 Psoriasis Scalp Severity Index

The PSSI is a grading system for scalp psoriasis, which is similar to the PASI for generalized psoriasis. The scale for PSSI ranges from 0 (absent) to 4 (very severe) for each of the three categories of erythema, desquamation and thickness, which are rated separately. The individual scores are then added and multiplied by a number based on the area of the scalp that is covered by psoriasis. The final PSSI score can range from 0 to 72.

The PSSI is provided in Appendix 3.

7.3.2.4 Palmoplantar Psoriasis Physician's Global Assessment (PP PGA)

The investigator or designee will assess the subject's palmar and plantar surfaces using the PP PGA score. The PP PGA is provided in Appendix 4.

7.3.2.5 Pruritus Numerical Rating System

The subject will be asked to rate the intensity of their pruritus using the Pruritus NRS. The Pruritus NRS will be used to assess pruritus intensity over the previous 24 hours. It is a commonly used instrument with demonstrated high reliability and concurrent validity (Phan, 2012; Reich, 2009). The NRS records the subject's perceptions of their pruritus and can be used to monitor changes over time.

7.3.3 Health-related Quality of Life Assessments

Health-related QoL assessments will be performed at the visits specified in Table 1-1.

7.3.3.1 Dermatology Life Quality Index

The subject will be asked to complete the DLQI, which is a validated questionnaire consisting of 10 questions relating to the degree to which the subject's skin condition affects their daily activities (Finlay 1994). The DLQI is provided in Appendix 5.

7.3.3.2 12-Item Short Form Survey

The SF-12 questionnaire contains a set of generic, coherent, and easily administered patient-reported quality-of-life measures that are useful for the monitoring and assessment of care outcomes in adult subjects. The SF-12 is provided in Appendix 6.

7.3.3.3 Quick Inventory of Depressive Symptomatology-Self Report (16 Items)

The Quick Inventory of Depressive Symptomatology – Self Report is a questionnaire designed to be filled out by the subject to assess the severity of depressive symptoms. The Quick Inventory of Depressive Symptomology – Self Report is provided in Appendix 7.

7.3.3.4 Work Productivity and Activity Impairment Questionnaire: Psoriasis

The Work Productivity and Activity Impairment (WPAI) questionnaire is an instrument designed to measure impairments in work and in activities.

The Work Productivity and Activity Impairment Questionnaire: Psoriasis (WPAI:PSO) is provided in Appendix 8.

7.3.3.5 Health Economics and Outcomes Research

The HEOR evaluation will be performed by asking three questions at Baseline, Week 12, Week 16, Week 24/ETV, and Week 25 Visit. The questions are the following:

- **Baseline visit**
  - How many times, in the past 3 months, have you been to any physician's office or urgent care clinic?
    - Please state reason for each visit
  - How many times, in the past 3 months, have you seen a nurse practitioner, a physician assistant, a psychologist, a naturopath, an acupuncturist, a chiropractor, or other healthcare professional (HCP)?
    - Please state reason for each visit
  - How many times, in the past 3 months, have you received care from a health professional in your home?
    - Please state reason for each visit

- **12 weeks, 16 weeks, 24 weeks and 25 weeks**
  - How many times, since you started the study medication, have you been to any physician's office or urgent care clinic, other than the regular assessment appointments as part of the clinical trial?
    - Please state reason for each visit
  - How many times, since you started the study medication, have you seen a nurse practitioner, a physician assistant, a psychologist, a naturopath, an acupuncturist, a chiropractor, or other healthcare professional (HCP)?
    - Please state reason for each visit
  - How many times, since you started the study medication, have you received care from a health professional in your home?
    - Please state reason for each visit

7.4 Assessment of Pharmacokinetics

No pharmacokinetics determinations will be assessed during this study.

7.5 Assessment of Safety

7.5.1 Adverse Events

7.5.1.1 Adverse Events Assessments

An AE is an untoward medical occurrence in any subject during the study which does not necessarily have a causal relationship with the study drug treatment. Adverse events can be categorized as treatment-emergent or treatment-related. All AEs will be recorded and will be documented in the eCRF and will be captured from the time of intake of study drug. All serious adverse events (SAEs) will be captured from the time of signing the ICF and must be reported to the sponsor within 24 hours of awareness. The condition of the subject will be monitored throughout the study for any signs or symptoms. The occurrence of AEs should be sought by

nondirective questioning of the subject at each visit during the study. All AEs will be collected as:

- The subject's response to questions about their health
- Symptoms spontaneously reported by the subject
- Clinically relevant changes and abnormalities observed by the investigator (eg, local and systemic tolerability, laboratory measurements, results of physical examinations)

If a Medical History condition worsens or increases in frequency after the first dose of IP, it should be recorded as an AE in the eCRF. If an AE worsens in intensity, it should be recorded as a new AE. Otherwise, it continues as the first report (counted as the same AE) until the subject is recovered.

The investigator or designee will record the following on the AE eCRF:

- AE and relevant clinical findings
- Time/date of onset
- Time/date of recovery
- Intensity
- Action taken on study drug/treatment
- Other action taken to treat the event
- Relation to study drug/treatment
- Seriousness of the AE

AEs requiring therapy must be treated with recognized standards of medical care to protect the health and well-being of the subject. Treatment due to an AE will be recorded.

Subjects who prematurely withdraw from the study for AEs are to be monitored for up to 30 days after the subject stopped study treatment or until the abnormal parameter resolves or stabilizes.

The outcome of an AE will be classified as recovered, recovered with sequelae, not yet recovered, or death.

7.5.1.2 Timing

Adverse events will be assessed at all study visits. Adverse events should be monitored by the investigator for up to 30 days after the subject has stopped study treatment or until the AE has resolved or stabilized.

Treatment-emergent AEs (TEAEs) include any untoward medical occurrence in a patient/subject or clinical investigation subject after administration of an investigational study treatment, which does not necessarily have to have a causal relationship with this treatment. A TEAE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the product, whether or not related to the medicinal (investigational) product. It could also include accidents and reasons for changes in medication (drug and/or dose), any medical, nursing or pharmacy consultation, or admission to hospital or surgical operations. Record TEAEs that occur after the first dose through 5 days after the last dose.

Treatment-related AEs are all TEAEs that are considered by the investigator as causally related to administration of the study drug.

7.5.1.3 Severity of Adverse Events

The investigator is to classify the severity (intensity) of an AE according to the following definitions:

- Mild – The subject was aware of the signs and symptoms but the signs and symptoms were easily tolerated.
- Moderate – The signs and symptoms were sufficient to restrict, but did not prevent, usual daily activity for the subject.
- Severe – The subject was unable to perform usual daily activity.

The maximum intensity of an AE (mild, moderate, or severe) will be assessed taking into account the possible range of intensity of the symptom(s).

The severity of diarrhea and lymphocytopenia will be graded using a modified common terminology criteria for adverse events (CTCAE), Version 4.03 (see Appendix 9). If the subject reports that they are experiencing diarrhea, they will be presented with the Bristol Stool Chart and asked to identify the consistency (see Bristol Stool Chart Appendix 10). Only Type 7 on the Bristol Stool Chart is considered diarrhea. The frequency of Type 7 diarrhea is then used to determine the CTCAE grade. All subjects will be provided with educational materials at Baseline to help prepare them for the potential GI-related adverse events. All subjects will be asked at Baseline to assess the average frequency of their bowel movements for the past 15 days and the general consistency of the stool using the Bristol Stool Chart.

7.5.1.4 Relationship of an Adverse Event to Study Treatment

The investigator is to classify the relationship of an AE to the IP using good clinical judgment and the following definitions:

Not Related	The AE is clearly explained by another cause not related to the study product
Probably Not Related	A potential relationship between study product and the AE could exist (ie, the possibility cannot be excluded), but the AE is most likely explained by causes other than the study agent
Possibly Related	The AE and administration of study product are temporally related, but the AE can be explained equally well by causes other than the study product
Probably Related	The AE and use of study product are temporally related, and the AE is more likely explained by study product than by other causes
Definitely Related	The AE and use of study product are related in time, and a direct association can be demonstrated

Adverse events commonly observed in previous clinical studies with PPC-06 include GI disorders, including diarrhea, nausea, and abdominal pain, and flushing. As a class, FAEs are known to have an effect on lymphocyte and eosinophil counts. Reversible lymphopenia and transient eosinophilia are frequently observed with both Fumaderm and Tecfidera treatment.

7.5.1.5 Adverse Event of Special Interest (AESI)

If the subject complains of any kind of neurological symptoms (such as aphasia, clumsiness, weakening of arms and legs or any new neurological signs or symptoms) during the scheduled study visits or at any time point during the study, the subject will be evaluated at the site for any neurological dysfunction. If the site evaluation for neurological dysfunction is positive or equivocal, the subject will be referred to a neurologist for consultation. If the subject is negative for PML after examination by the neurologist, the subject will continue in the study. If required, the PML experts will be consulted to assess and monitor, as the case may be. The study drug will be stopped in the subject only if recommended by the PML expert.

Stopping Rules:

The potential event of PML will be carefully managed by utilizing the below stopping criteria. If one or more of the below criteria are met, study drug will be permanently discontinued and the subject will be scheduled for an ETV followed by Safety Follow-up visits 1 week (± 3 days) after the last dose of study drug.

- Lymphocytes <500/mm3 in one reading;
- Lymphocytes <800/mm3 in 3 consecutive visits 4 weeks apart; Lymphocyte count can be repeated in the interim period. If the interim lymphocyte counts are higher than 800/cu.mm, then the PI with concurrence from Medical monitor, will decide if the subjects should stay in the study or discontinued from the study.
- When recommended by the PML expert.

Blood collection for lymphocyte subset & Ab titer can be collected at any study visit if the subject shows signs of PML.

7.5.2 Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect, or is an important medical event

The death of a subject enrolled in a study is per se not an event, but an outcome. Any event resulting in a fatal outcome must be fully documented and reported, regardless of the causality relationship to the IP.

The term life-threatening refers to an AE in which the subject was at immediate risk of death at the time of the event. It does not refer to an event, which may have caused death, if it was more severe.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of important medical events include AEs, which suggest a significant hazard, contraindication or precaution, occurrence of malignancy, or development of drug dependency or drug abuse.

Any SAE, whether or not deemed drug-related or expected, must be reported immediately to the sponsor's designee as soon as it becomes known to the investigator and not later than within 24 hours of his/her knowledge of the occurrence of an SAE. The investigator will document such events in the best possible detail on the SAE Report Form to be transmitted to the sponsor's designee.

An IND Safety Report (INDSR) is an SAE that is both unexpected (not consistent with the current Investigator's Brochure/product information) and for which there is evidence to suggest a causal relationship between the drug and the AE. The Institutional Review Board (IRB) will be informed of INDSRs according to local requirements. All investigators participating in the trial will also be notified of unexpected SAEs. The sponsor will report SAEs and other events requiring expedited reporting to regulatory authorities as required.

Investigator instructions for reporting SAEs are provided in Section 13.2.

7.5.3 Safety Laboratory Assessments

Blood and urine samples for laboratory tests (hematology, serum biochemistry, and urinalysis) will be collected as specified in Table 1-1. Clinical laboratory specimens will be analyzed by a central licensed and accredited laboratory facility according to the laboratory's standard operating procedures.

If any of the laboratory parameters of interest show a significant shift from baseline, subjects will then be scheduled for an interim visit within 2 weeks to repeat the laboratory measurements.

Non-fasting blood samples will be obtained at each visit for laboratory analysis of serum glucose, lipid panel, hsCRP, and PD study.

No blood is to be collected for the PD study at Screening.

Blood samples for serology assessment (HIV, HBsAg, Anti-HBc, and HCV) will be obtained at Visit 1 (Screening).

Lymphocyte subsets and antibody titer will be collected for safety assessments per Table 1-1.

The routine clinical laboratory tests to be performed are provided in Table 7-2.

The investigator may collect additional blood or urine samples to repeat any laboratory test that was abnormal post-dosing, or was within normal limits at Baseline, and is considered clinically significant. Abnormal laboratory results at the last scheduled visit may require additional collection of samples on an "as needed" basis until: a) the values return to the baseline value, b) the values are within normal limits, c) the values are clinically stable, or d) the investigator determines that further follow-up is unnecessary. The investigator will record the date and time of all additional samples collected. If the investigator establishes a clear explanation for the laboratory abnormality, he/she will record this explanation in the eCRFs.

Blood will also be collected and evaluated for PD study per Table 1-1.

Table 7-2 Routine Clinical Laboratory Assessments

Hematology

- Platelet Count
- RBC Count
- WBC Count (absolute)
- Lymphocytes (absolute)
- Neutrophils (absolute)
- Monocytes (absolute)
- Hemoglobin
- Hematocrit

RBC Indices:

- MCV
- MCHC
- MCH

Automated WBC Differential:

- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils

- Lymphocyte subset (collected and will be assessed)
- Antibody titer (collected and stored with assessment done as required)

Chemistry

- Sodium
- Potassium
- Chloride
- Bicarbonate
- BUN
- Creatinine
- AST (SGOT)
- ALT (SGPT)
- Creatine Kinase
- Alkaline Phosphatase
- GGT
- LDH
- Total Bilirubin
- Direct Bilirubin
- Total Protein
- Glucose (non-fasting)
- Albumin
- Cholesterol
- Triglycerides
- HDL Cholesterol
- LDL Cholesterol
- Calcium
- Phosphorus
- Uric Acid
- Magnesium
- Creatinine Clearance

Routine Urinalysis

- Appearance, color
- pH, specific gravity
- Glucose, blood, bilirubin, leukocyte esterase, ketones, nitrates
- Urine protein, urine creatinine, protein:creatinine ratio
- Microscopic examination (if indicated per clinical laboratory standards)

Serology (Visit 1/Screening only)

- HIV
- HBsAg and Anti-HBc
- HCV

7.5.4 Pregnancy Testing

All female subjects will undergo a serum pregnancy test at the screening visit. Female subjects of child-bearing potential will undergo a urine pregnancy test at the baseline visit before the subject is randomized. If either pregnancy test is positive, the subject will not be permitted to enroll in the study.

Urine pregnancy tests will be performed as per the study schedule. At the investigator's discretion, additional testing for pregnancy may be performed for verification purposes. The

pregnancy tests must have a sensitivity of at least 25 mIU/mL. If there is a suspicion of pregnancy at any time during the study, a urine sample will be obtained and tested. Should a subject become pregnant during the study, treatment must be immediately discontinued. Subjects should continue with non-treatment and/or follow-up visits.

All pregnancies should be immediately reported to the sponsor/Contract Research Organization (CRO)/Medical Monitor and followed through to resolution (ie, delivery, miscarriage, or abortion). The report should be submitted within the same timelines as an SAE (within 24 hours of knowledge), although a pregnancy per se is not considered an SAE.

7.5.5 Vital Signs

Measurements of vital signs, including blood pressure, pulse rate, and respiratory rate, will be taken at every visit with the subject seated.

7.5.6 Physical Examination

A complete physical examination including assessments of the head, eyes, ears, nose, throat, skin, neck (including thyroid), lungs, cardiovascular, abdomen, lymph nodes and extremities will be obtained at Screening. Weight (in kg), height (in cm) and waist circumference (in cm) will also be measured.

An abbreviated physical exam including changes since the Screening Visit with focus on previously noted abnormalities in organ systems, including skin, will be completed at Baseline/Visit 2 and at all post-Baseline visits. Weight will also be measured.

Abnormalities noted during the Screening or Baseline physical exams should be recorded on the Medical History eCRFs. Any abnormalities noted on the physical exam following the first dose of study drug should be recorded as an AE, as appropriate.

7.5.7 Electrocardiogram

A 12-lead electrocardiogram (ECG) will be recorded at the visits specified in Table 1-1.

7.6 Appropriateness of Measurements

The methodology used in this study to determine efficacy and safety are the standardized and most widely accepted methods for evaluating safety and efficacy in studies of plaque psoriasis.

8. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE STATISTICAL AND ANALYTICAL PLANS

8.1 General Considerations for Data Analysis

The methodology presented in this section represents a brief overview of the statistical methods that will be fully detailed in the statistical analysis plan (SAP). The SAP will be finalized before the database is locked and unblinded. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

Study sites will be pooled into analysis centers for the efficacy analyses. The composition of pooled analysis centers will be finalized before the database is locked and unblinded.

All statistical analyses will be performed using SAS statistical software (Version 9.2 or above). Statistical significance will be tested at the 2-sided 5% level. Subgroup analyses (eg, prior biologic use) may be performed.

Data collected in this study will be presented using summary tables, figures, and subject data listings. Summary tables will present data by treatment group and, if applicable, by time of collection. Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized by frequencies and percentages. Figures will be used to support the presentation of certain data.

8.2 Sample Size and Power Considerations

It was determined that a sample size of 100 subjects per treatment group would detect a significant difference in proportion of PASI-75 and IGA responders from Baseline to Week 24 between each dose group of PPC-06 and placebo group, assuming a 15% response rate for the placebo group and 45% for PPC-06 at Week 24. To provide sufficient evidence of treatment effect, both PASI and IGA based response rate have to be rejected at the same significance level. The hypothesis testing for the 3 dose groups will be conducted sequentially from high to low dose; therefore, the 2-sided Type I error rate from a chi-squared test remains at the 0.05 level. Assuming 50% dropout rate, about 100 subjects per treatment arm will be randomized to get approximately 50 completers in each treatment arm. The total sample size of 400 subjects will yield at least 84% power for hypothesis testing of the co-primary endpoints of a difference in PASI-75 and IGA responders from Baseline to Week 24 between PPC-06 doses and placebo.

8.3 Analysis Populations

The analysis populations include the following:

- The safety population will include all subjects who receive at least one dose of IP. The safety population is the population used for all safety analyses.
- Full Analysis Set (FAS) - All randomized subjects who receive at least one dose of investigational product and have at least one post dose efficacy assessment. The FAS population will be the primary population for the efficacy analyses.
- The Per Protocol (PP) population will include subjects in the FAS population who complete the study without any major protocol violations. The composition of the PP population will be determined and documented in blind reviews of the database conducted prior to unblinding the study database.

8.4 Background and Demographic Characteristics

Demographic data that will be summarized include age, gender, race, weight, waist circumference, and BMI. Baseline characteristics assessments include the pre-dosing assessments for the following variables: PASI, BSA, and IGA. Demographic and Baseline characteristics will be summarized by treatment group.

Any variables found to be imbalanced across treatment groups at Baseline may be included as covariates or be used as subgroup levels in exploratory efficacy analyses. Full details of the Baseline analyses will be described in the SAP.

8.5 Study Medication/Visit Compliance

The number of doses received by each subject and the number of days exposed to study medication will be summarized by treatment group and study period (titration, treatment, overall) using summary statistics (mean, standard deviation [SD], median, minimum, and maximum), and categorically.

The percent of subjects compliant with study medication at each visit will be presented by study period and overall.

Following are the compliance parameters:

- Total number of tablets taken during the titration period (Week 1-5), defined as number of dispensed tablets from blister wallets minus number of returned tablets from blister wallets.
- Total number of tablets taken during the treatment period (Week 6 – 24), defined as total number of dispensed tablets from bottles minus total number of returned tablets from bottles.
- Number of tablets taken per bottle during the treatment period (Weeks 6 - 24), defined as number of dispensed tablets per bottle (total of 4 bottles per visit) minus number of returned tablets per bottle (total of 4 bottles per visit).
- Total number of tablets taken, defined as the summation of number of tablets taken during the titration and the treatment period.
- Percent compliance will be calculated as the number of tablets taken divided by the expected number of tablets, as defined for the titration period, treatment period and overall.
- Subject compliance, defined as 80% - 120% (inclusive) in percent. If the percentage of study medication compliance is unknown, the subject is assumed to be non-compliant with study medication.
- The average daily dose of IP received can be calculated as the number of tablets divided by the number of days exposed to study medication.

- The average daily dose of IP received by each subject will be summarized by visit, treatment group using summary statistics (mean, SD, median, minimum, and maximum), for the overall period.

8.6 Prior and Concomitant Therapy

Prior and concomitant medication information for all randomized subjects will be presented in a by-subject listing. Summary tables will be presented by Anatomical Therapeutic Chemical Classification System (ATC) therapeutic category and product based on WHO-DD coding.

8.7 Analysis of Efficacy

8.7.1 Co-Primary Efficacy Endpoint(s)

The co-primary efficacy endpoints are as follows:

- The proportion of subjects who achieve a reduction of 75% or greater from Baseline in the Psoriasis Area and Severity Index (PASI-75) at the end of Week 24
- The proportion of subjects who achieve an IGA score of clear or almost clear (IGA score 0 or 1) at the end of Week 24

The null hypothesis to be tested for the primary efficacy endpoint is that the proportion of subjects who achieve PASI-75 and IGA success is not different between the subjects treated with PPC-06 and placebo. The alternative hypothesis is that the proportion of subjects who achieve PASI-75 and IGA success at Week 24 for placebo is different from PPC-06. Each of the PPC-06 doses will be compared with placebo separately.

Each of the dichotomized endpoints, PASI-75 response (Yes/No) and the IGA response, at Week 24 will be analyzed using a logistic regression model with treatment, baseline BMI, and pooled analysis center as factors. Additional factors may be included in the models. Each of the PPC-06 doses will be compared to placebo separately.

To provide sufficient evidence of treatment effect, both PASI and IGA based response rate have to be rejected at the same significance level. The hypothesis testing for the 3 dose groups will be conducted sequentially from high to low dose; therefore, the 2-sided Type I error rate from a chi-squared test remains at the 0.05 level.

8.7.2 Secondary Efficacy Endpoints

The secondary endpoints are the following

- Percent change from Baseline in Total PASI Score by Visit;
- Proportion of subjects who achieve PASI-50 and PASI-75 by Visit;
- Proportion of subjects who achieve an IGA score of clear or almost clear by Visit;
- Absolute and percent change from Baseline in percent of affected BSA by Visit;

- For applicable subjects, change from baseline by visit in NAPSI of the target fingernail, PSSI, and PP PGA;
- Absolute and percent change from baseline in pruritus NRS by visit
- Time to achieving a PASI 75 response;
- Time to achieving an IGA score of 0 or 1;

The quality of life endpoints are the following:

- Change from Baseline by Visit in DLQI Total Score, SF-12, QIDS-SR16, and WPAI: PSO;
- Summary of HEOR questions by visit;

Secondary efficacy variables will be analyzed as follows:

Categorical secondary efficacy endpoints will be summarized at each visit using the number and percentage of subjects within each category for each treatment group. A same logistic regression model as used for the primary endpoint will be performed including treatment, baseline BMI, and pooled analysis center as factors. Additional factors may be included in the models. Each treatment will be compared to placebo separately as described in the primary analysis.

Continuous secondary efficacy endpoints will be summarized descriptively and analyzed using an Analysis of Variance (ANOVA) including factors for treatment, baseline BMI, and pooled analysis center. Each treatment will be compared to placebo separately as described in the primary analysis. Additional factors along with interaction terms may be included in the models.

All secondary efficacy analyses will be performed on the FAS and PP populations. Subgroup analyses may also be performed.

All QoL endpoints will be summarized by visit and treatment group using descriptive statistics.

8.7.3 Handling of Missing Values/Censoring/Discontinuations

The primary population for all efficacy analyses will be the FAS population.

For the analyses of the primary endpoints (PASI-75 and IGA) based on the FAS population, several methods will be used to impute missing data, including, multiple imputation (MI), modified non-responder imputation (mNRI), and last-observation-carried forward (LOCF). MI will be the primary imputation method. Sensitivity analyses using LOCF and m-NRI will be performed to assess the robustness of alternate imputation assumptions. In particular, subjects

who used rescue medications or who discontinue due to unsatisfactory therapeutic effect will be included in PP population. These subjects will be considered as treatment failures (i.e., non-responder for both PASI-75 and IGA) for all time points after the initiation of rescue medications or subject discontinuation.

MI: Missing data will be imputed using multiple imputations. MI will be implemented for all subjects with missing data, including those who used rescue medications and those who discontinued due to unsatisfactory therapeutic effect.

MI for missing PASI scores : Intermittent missing values of PASI scores will be imputed separately for each treatment group using the Markov Chain Monte Carlo (MCMC) method, generating 50 copies of the imputed dataset with monotonic missing pattern. For each of the 50 datasets, missing values at scheduled visits (Weeks 4, 8, 12, 16, 20 and 24) will be imputed using a linear regression model. The imputations will include the following variables: baseline BMI, baseline PASI score, and PASI scores at the previous scheduled visits. SAS Proc MI will be used. Imputed PASI-75 response (Yes/No) will be derived for each imputed dataset.

MI for missing IGA scores : The imputation of post-baseline IGA scores will be performed following a similar approach as described for PASI scores. Intermittent missing IGA scores will be imputed separately for each treatment group using the Markov Chain Monte Carlo (MCMC) method where 50 copies of the dataset with monotonic missing pattern will be generated. For each of the 50 datasets, missing values at scheduled visits (Weeks 4, 8, 12, 16, 20 and 24) will be imputed using a logistic regression model including baseline BMI, baseline IGA score, and IGA scores at the previous scheduled visits. SAS Proc MI using the logistic regression method for monotone data will be used for the imputation. IGA Treatment Success status (Yes/No) will then be derived for each imputed dataset.

The imputation of missing post-baseline BSA, NAPSI, and NRS scores will be performed using a similar method as described for PASI. The imputation of missing post-baseline PSSI and PP PGA scores will be performed using a similar method as described for IGA. No imputation will be done to the health-related quality of life endpoints or safety endpoints and only observed values will be analyzed.

mNRI: Subjects who used rescue medications or discontinued due to unsatisfactory therapeutic effect are considered as treatment failures (i.e., non-responder) for all time points after the intitaition of rescue medications or subject discontinuation. Other missing data are not to be imputed and are to be kept as missing.

LOCF: The last observed value will be carried forward for any subsequent missing values. Baseline values will not be carried forward.

All QoL endpoints will be analyzed using the OC approach. No other imputations will be made unless otherwise specified.

Note that Early Termination visit data will be analyzed at the closest visit where data are not obtained. Full details will be provided in the SAP.

8.7.4 Control of Multiplicity

For the primary efficacy analysis (PASI-75 and IGA), each of the PPC-06 doses will be compared with placebo separately, sequentially from high to low dose to maintain the Type-I error rate. Therefore, no adjustments for multiplicity will be performed.

8.8 Analysis of Safety

The assessment of safety will be based mainly on the frequency of AEs and on the number of laboratory values that fall outside of predetermined ranges. Adverse events will be presented in data listings and summarized by frequency and severity for each treatment group. Laboratory and vital sign data will be presented in data listings. Abnormal laboratory findings will be presented. The analysis of safety will be described in the SAP.

8.8.1 Adverse events

All AEs recorded during the study will be coded using the MedDRA coding dictionary. Adverse events that occurred after the first dose of study treatment are called TEAEs. The number and incidence of TEAEs will be summarized by MedDRA System Organ Class (SOC)/Preferred Term (PT), intensity/severity, and relationship to study drug/treatment. Deaths and non-fatal SAEs will be listed by subject and tabulated by PT.

8.8.2 Laboratory Evaluations

Clinical laboratory values will be reported as complete listings of individual subject data. All laboratory values will be classified as normal, low, or high based on normal ranges supplied by the laboratory. Subjects with values outside the normal range will be flagged and summarized using shift tables. A separate listing and table will identify and summarize subjects with markedly abnormal values. For quantitative measures, observed and changes in clinical laboratory values will be analyzed descriptively by time of collection and treatment group. Lymphocyte counts will also be summarized by clinical response at PASI-50 and PASI-75 at Week 24. Lymphocyte counts and hs-CRP will also be plotted against PASI scores by visit and treatment.

8.8.3 Vital Signs

Change in vital sign data will be classified as normal, low, high, based on a reference range. Observed and changes in vital sign parameters will be analyzed descriptively by time of collection and treatment group. Subjects with markedly abnormal changes will be listed and tabulated separately.

8.8.4 Cardiac Assessments

Data will be listed, notable values will be flagged, and any other information collected will be listed as appropriate. Subjects with markedly abnormal ECG changes will be listed and tabulated separately. Observed changes will be analyzed descriptively by time of collection and treatment group.

8.8.5 Other Safety Assessments

Concomitant medications/non-drug therapies taken during the study will be mapped to generic drug name and drug class. The number and percentage of subjects taking concomitant medications will be presented by treatment.

8.9 Futility Analysis

Futility analysis will be done when 50, 100 and 200 subjects complete the Double-Blind Treatment period. The analysis will be performed on blinded data.

8.10 Protocol Deviations and Violations

Protocol deviations will be identified on an ongoing basis and will be fully specified in InfoLink2, Novella Clinical's web-based Clinical Management System. Subjects with major protocol deviations will be excluded from the per protocol population. The assessment of all protocol deviations will be finalized prior to database lock. A subject with more than one major deviation per category will be counted only once for that category.

If there is discrepancy between protocol and Statistical Analysis Plan (SAP), SAP will supersede.

9. CHANGES IN THE PLANNED STUDY

9.1 Protocol Amendments

With the exception of administrative changes, any changes or additions to this clinical study protocol require a written protocol amendment that must be approved by the sponsor, the CRO, and the investigator(s) before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study, require additional approval by the IRB or IEC for each study center.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or the sponsor in the interests of preserving the safety of all subjects included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons, the sponsor should be notified and the IRB/IEC should be informed according to their reporting requirements.

9.2 Termination or Suspension of the Study

The sponsor reserves the right to terminate or suspend the study at any time. In case of premature termination or suspension of the study, the CRO project manager will promptly inform the investigators, regulatory authorities, and IRBs/IECs about the premature termination or suspension, including the reason for termination. In terminating the study, the sponsor and the investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

10. DATA HANDLING AND RECORD KEEPING

10.1 Recording of Data

10.1.1 Source Documents

Source data are all the information in original records and copies of original records of clinical findings, observations, or other activities in the study, which are necessary for the reconstruction and evaluation of the study. The identification of any data to be recorded directly on the CRFs is to be considered source data.

Study data collection procedures must ensure that each data element can be traced with a high level of confidence from its originator or recorder to its representation in the study database and then to its place in the analysis and report of study results. Once recorded, the study data must be protected from unauthorized modification or deletion, and all authorized modifications and deletions must be securely linked in the permanent record with their author, time of change, and reason for change (ie, the audit trail must be maintained).

The investigator will permit study-related monitoring, audit(s), IRB/IEC review(s) and regulatory inspection(s), with direct access to all the required source records.

The principal investigator will certify the data to be accurate and complete and will release the data for transmittal to the sponsor or CRO.

Source records need to be preserved for the maximum period of time permitted by local requirements (see Section 10.2). For each subject enrolled, the investigator will indicate in the source record(s) that the subject participated in the study.

10.1.2 Case Report Forms

The primary data collection tool for the study is an eCRF designed specifically for the study. For each subject enrolled in the study, an eCRF will be completed by the study coordinator and signed by the investigator or his/her designee. Some QoL assessments as well as some investigator efficacy assessments will be recorded directly into an electronic device which will serve as the source document; the data will then be transferred to the eCRF.

The investigator will be responsible for ensuring the accuracy of all data entered in the eCRFs. All eCRFs are to be completed in a timely manner.

Errors occurring in the eCRFs will be queried. Queries raised by data reviewers must be addressed by site personnel.

On request, the investigator will provide the sponsor with additional data relating to the study, or copies of relevant source records, duly anonymized (ie, subject's name is redacted).

10.2 Retention of Documents

The United States Food and Drug Administration (FDA)/International Conference on Harmonisation (ICH) regulations require all investigators participating in clinical drug trials to maintain detailed clinical data for one of the following periods:

- at least 2 years following the date on which a Marketing Application is approved by the FDA/applicable regulatory or health authority, or
- 2 years after the sponsor notifies the investigator that no further application is to be filed with the health authorities

Similarly, ICH guidelines require that essential documents be retained until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. European Union (EU) Directive 2001/63/EC requires that essential documents be retained for at least 15 years after completion or discontinuation of the trial.

To comply with these requirements, the investigator will not dispose of any records relevant to this study without either (1) written permission from the sponsor, or (2) providing an opportunity for the sponsor to collect such records. The investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study, including any data clarification forms received from the sponsor. Such documentation is subject to inspection by the sponsor or its agents, the FDA and/or other regulatory agencies.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Direct Access to Source Documents

As specified in the investigator's agreement, the investigator agrees to allow study-related monitoring, audit(s), IRB/IEC review(s) and regulatory inspection(s), with direct access to all the required source records, and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues.

11.2 Monitoring Procedures

The Clinical Study Monitor will contact and/or visit the investigator site periodically to verify the adherence to the protocol, the maintenance of study-related source records, and the completeness and accuracy of all CRF entries compared to source data. The investigator will cooperate with the study monitor to ensure that any discrepancies that may be identified are resolved.

11.3 Audit and Inspection

The investigator will make all the study-related source data and records available to a quality assurance auditor mandated by the sponsor, or to domestic or foreign regulatory inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects have been adequately protected, and that all data relevant for the evaluation of the IP have been processed and reported in compliance with Good Clinical Practice (GCP)/ICH and applicable regulatory requirements.

The investigator is to notify the sponsor/CRO immediately of any inspection by regulatory authorities or IRBs.

12. ETHICS

12.1 Ethical Conduct of the Study

This study must be carried out in compliance with the protocol and the applicable laws and regulatory requirements of the FDA. The study must be conducted in accordance with the ethical principles originating from the Declaration of Helsinki and amendments and the ICH-GCP guidelines.

12.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC)

This protocol, the proposed ICF, and other information for subjects must be reviewed and approved by an IRB or IEC, before the start of the trial, in compliance with local regulations. This committee must also approve any amendments to the protocol, other than administrative ones, before initiation of the amendment procedures.

12.3 Subject Information and Consent

Before participation in the study, each subject is required to provide written consent to participate in the study. No study-specific procedures will be performed before a subject's informed consent is obtained.

12.4 Disclosure and Confidentiality

12.4.1 Confidentiality of Study Documentation

By signing the protocol, the investigator agrees to keep all information provided by the sponsor in strict confidence and to request similar confidentiality from his/her staff and the IRB or IEC.

Study documents provided by the study sponsor (ie, protocols, Investigators' Brochures, CRFs and other material) will be stored appropriately to ensure their confidentiality. The information provided by the sponsor to the investigator may not be disclosed to others without direct written authorization from the sponsor, except to the extent necessary to obtain informed consent from subjects who wish to participate in the trial.

12.4.2 Privacy of Individual Health Information

The investigator will undertake to protect the privacy of all individually identifiable health information except as specifically authorized by each individual subject through the written informed consent. The Informed Consent document will include a request of the subject's consent to release the collected data for research purposes in such a way that the individual's identity remains masked. While all data records will be identified by the corresponding subject number, the identity of the subject will be held in confidential source documents at the study site. All study personnel with access to this information are legally bound not to disclose such information.

13. EMERGENCY PROCEDURES

13.1 Emergency Unblinding

Unblinding by study personnel should only be performed in emergencies where knowledge of the subject's treatment assignment is essential for further management of the subject's medical care. Unblinding a subject's treatment assignment under any other circumstances will be considered a protocol violation.

The investigator should assess the relationship of any AEs to administration of the IP prior to unblinding.

The investigator is strongly encouraged to contact the study Medical Monitor before unblinding any subject's treatment assignment, but must do so within 1 working day after the unblinding. The subject's treatment code should not be communicated to the Medical Monitor or designee. The unblinding will be documented by the investigator.

13.2 Reporting of Serious Adverse Events and Pregnancies

13.2.1 Contact Person(s) and Number(s)

Serious adverse events and pregnancies must be reported immediately (ie, not later than 24 hours after first knowledge) to the sponsor's designee, who then forwards the information to the Medical Monitor and the sponsor.

The telephone and fax numbers of the study personnel to be contacted in the event of an SAE are provided to each site and are updated as required.

Dr. Reddy's Laboratories Ltd, Clinical Pharmacovigilance:

Shahida Hasan, MD

Associate Director

Fax: 908-450-1510 / 1-877-445-3741

Email: sae@drreddys.com

13.2.2 Reporting Procedures

Serious Adverse Events

For each SAE, the investigator will complete a Serious Adverse Event Report Form and assess the relationship of each SAE to study treatment. The completed form(s) should be sent electronically to the sponsor's designee within 24 hours of first knowledge of the SAE.

Follow-up reports regarding the status of the SAE and the subject's subsequent course should be submitted until the SAE has subsided, the condition stabilized (in the case of persistent impairment), the subject receives alternative therapy, or the subject dies. The form and fax confirmation will be retained. Contacts for reporting SAEs and other safety concerns are provided to each site.

14. PUBLICATION POLICY

Written permission must be obtained from the Sponsor prior to submission to a publication or presentation.

If the data merit, the Investigator and the Sponsor will discuss the preparation of a manuscript for publication in a peer-reviewed professional journal or an abstract for presentation, oral or written, to a learned society or symposium. Authorship should reflect work done by the Investigators and personnel of the Sponsor, in accordance with generally recognized principles of scientific collaboration.

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16. APPENDICES

Appendix 1 Psoriasis Area and Severity Index (PASI)

Appendix 2 Nail Psoriasis Severity Index (NAPSI)

Appendix 3 Psoriasis Scalp Severity Index (PSSI)

Appendix 4 Palmoplantar Psoriasis Physician's Global Assessment (PP PGA)

Appendix 5 Quality of Life Assessment: Dermatology Life Quality Index (DLQI)

Appendix 6 Quality of Life Assessment: SF-12

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Appendix 10 Bristol Stool Chart

Appendix 1 Psoriasis Area and Severity Index (PASI)

PASI consists of two major steps:
1) calculating the BSA covered with lesions and
2) assessment of the severity of lesions, including assessing the erythema (redness), induration (thickness) and scaling.

All calculations are combined into a single PASI score in the range of 0 (no psoriasis on the body) and up to 72 (the most severe case of psoriasis).

Intensity
A representative area of psoriasis is selected for each body region. The intensity of redness, thickness and scaling of the psoriasis is assessed as none (0), mild (1), moderate (2), severe (3) or very severe (4).

Calculation for intensity
The three intensity scores are added up for each of the four body regions to give subtotals A1, A2, A3, A4.
Each subtotal is multiplied by the body surface area represented by that region.
A1 x 0.1 gives B1
A2 x 0.2 gives B2
A3 x 0.3 gives B3
A4 x 0.4 gives B4

Area
The percentage area affected by psoriasis is evaluated in the four regions of the body (see below). In each region, the area is expressed as nil (0), 1-9% (1), 10-29% (2), 30-49% (3), 50-69% (4), 70-89% (5) or 90-100% (6):

Head and neck
Upper limbs
Trunk
Lower limbs

Calculations for area
Each of the body area scores is multiplied by the area affected.
B1 x (0 to 6)= C1
B2 x (0 to 6)= C2
B3 x (0 to 6)= C3
B4 x (0 to 6)= C4

Total score
The PASI score is C1 + C2 + C3 + C4

Appendix 2 Nail Psoriasis Severity Index (NAPSI)

The **Nail Psoriasis Severity Index (NAPSI)** is a numeric, reproducible, objective, simple tool for evaluation of nail psoriasis. This scale is used to evaluate the severity of nail bed psoriasis and nail matrix psoriasis by area of involvement in the nail unit

- NAPSI is used to assign a score to each nail for nail bed and nail matrix psoriasis (Rich 2003):
- nail plate is divided into quadrants by imaginary longitudinal and horizontal lines
    - nail plate is assessed for nail matrix psoriasis by the presence of any feature of nail matrix psoriasis, including nail pitting, leukonychia, red spots in the lunula, and crumbling in each quadrant of the nail
    - nail bed psoriasis is assessed by the presence of any features of nail bed psoriasis, including onycholysis, oil drop (salmon patch) dyschromia, splinter hemorrhages, and nail bed hyperkeratosis in each quadrant of the nail
    - score is 0 if the findings are not present, 1 if they are present in 1 quadrant of the nail, 2 if present in 2 quadrants of a nail, 3 if present in 3 quadrants of a nail, and 4 if present in 4 quadrants of a nail
        - thus each nail has a matrix score (0-4) and a nail bed score (0-4), and the total nail score is the sum of those 2 individual scores (0-8)
- All fingernails will be scored at Baseline and a target nail will be selected, which will be the nail with the highest score. Only the target nail will be evaluated at subsequent visits.

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Appendix 3 Psoriasis Scalp Severity Index (PSSI)

Psoriasis Scalp Severity Index (PSSI)

Descriptor	Score Range	Score
Erythema (E)	0 - 4	
Induration (I)	0 - 4	
Scaling (S)	0 - 4	
Area scoring	0 - 6	

Descriptors for severity:

0= None

1= Slight

2= Moderate

3= Marked

4= Severe

Area scoring criteria:

1= >0 to <10%, 2= 10 to <30%, 3= 30 to <50%, 4= 50 to <70%, 5= 70 to <90%, 6= 90 to 100%

Final score = (E+I+S) multiplied by area score

Appendix 4 Palmoplantar Psoriasis Physician's Global Assessment (PP PGA)

Palmoplantar Psoriasis Physician's Global Assessment (PP PGA) of Disease Severity

Score	Grade	Definition
0	Clear	No signs of plaque psoriasis on hands and/or feet
1	Almost clear	Just perceptible erythema and just perceptible scaling on the hands and/or feet.
2	Mild	Light pink erythema with minimal scaling with or without pustules on hands and/or feet
3	Moderate	Dull red, clearly distinguishable erythema with diffuse scaling and thickening of the skin, with or without fissures and with or without pustule formation on the hands and/or feet.
4	Severe	Deep, dark red erythema with clearly obvious diffuse scaling and thickening and numerous fissures with or without pustule formation on hands and/or feet.

Appendix 5 Quality of Life Assessment: Dermatology Life Quality Index (DLQI)

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date: Score: ☐

Name: Diagnosis:

Address:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please check one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your 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 **yard?**	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.

Appendix 6 Quality of Life Assessment: SF-12

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
b Climbing several flights of stairs	☐ 1	☐ 2	☐ 3

3. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. **These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Appendix 7 Quick Inventory of Depressive Symptomatology (Self-Report)

SELF-REPORT QUICK INVENTORY OF DEPRESSIVE SYMPTOMATOLOGY (QIDS-SR$_{16}$)

Name _____ Date _____

Please circle the one response to each item that best describes you for the past seven days.

1. Falling Asleep:
   - 0 I never take longer than 30 minutes to fall asleep.
   - 1 I take at least 30 minutes to fall asleep, less than half the time.
   - 2 I take at least 30 minutes to fall asleep, more than half the time.
   - 3 I take more than 60 minutes to fall asleep, more than half the time.

2. Sleep During the Night:
   - 0 I do not wake up at night.
   - 1 I have a restless, light sleep with a few brief awakenings each night.
   - 2 I wake up at least once a night, but I go back to sleep easily.
   - 3 I awaken more than once a night and stay awake for 20 minutes or more, more than half the time.

3. Waking Up Too Early:
   - 0 Most of the time, I awaken no more than 30 minutes before I need to get up.
   - 1 More than half the time, I awaken more than 30 minutes before I need to get up.
   - 2 I almost always awaken at least one hour or so before I need to, but I go back to sleep eventually.
   - 3 I awaken at least one hour before I need to, and can't go back to sleep.

4. Sleeping Too Much:
   - 0 I sleep no longer than 7-8 hours/night, without napping during the day.
   - 1 I sleep no longer than 10 hours in a 24-hour period including naps.
   - 2 I sleep no longer than 12 hours in a 24-hour period including naps.
   - 3 I sleep longer than 12 hours in a 24-hour period including naps.

5. Feeling Sad:
   - 0 I do not feel sad
   - 1 I feel sad less than half the time.
   - 2 I feel sad more than half the time.
   - 3 I feel sad nearly all of the time.

6. Decreased Appetite:
   - 0 There is no change in my usual appetite.
   - 1 I eat somewhat less often or lesser amounts of food than usual.
   - 2 I eat much less than usual and only with personal effort.
   - 3 I rarely eat within a 24-hour period, and only with extreme personal effort or when others persuade me to eat.

7. Increased Appetite:
   - 0 There is no change from my usual appetite.
   - 1 I feel a need to eat more frequently than usual.
   - 2 I regularly eat more often and/or greater amounts of food than usual.
   - 3 I feel driven to overeat both at mealtime and between meals.

8. Decreased Weight (Within the Last Two Weeks):
   - 0 I have not had a change in my weight.
   - 1 I feel as if I've had a slight weight loss.
   - 2 I have lost 2 pounds or more.
   - 3 I have lost 5 pounds or more.

9. Increased Weight (Within the Last Two Weeks):
   - 0 I have not had a change in my weight.
   - 1 I feel as if I've had a slight weight gain.
   - 2 I have gained 2 pounds or more.
   - 3 I have gained 5 pounds or more.

10. Concentration/Decision Making:
    - 0 There is no change in my usual capacity to concentrate or make decisions.
    - 1 I occasionally feel indecisive or find that my attention wanders.
    - 2 Most of the time, I struggle to focus my attention or to make decisions.
    - 3 I cannot concentrate well enough to read or cannot make even minor decisions.

11. View of Myself:

    0 I see myself as equally worthwhile and deserving as other people.
    1 I am more self-blaming than usual.
    2 I largely believe that I cause problems for others.
    3 I think almost constantly about major and minor defects in myself.

12. Thoughts of Death or Suicide:

    0 I do not think of suicide or death.
    1 I feel that life is empty or wonder if it's worth living.
    2 I think of suicide or death several times a week for several minutes.
    3 I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life.

13. General Interest:

    0 There is no change from usual in how interested I am in other people or activities.
    1 I notice that I am less interested in people or activities.
    2 I find I have interest in only one or two of my formerly pursued activities.
    3 I have virtually no interest in formerly pursued activities.

14. Energy Level:

    0 There is no change in my usual level of energy.
    1 I get tired more easily than usual.
    2 I have to make a big effort to start or finish my usual daily activities (for example, shopping, homework, cooking or going to work).
    3 I really cannot carry out most of my usual daily activities because I just don't have the energy.

15. Feeling slowed down:

    0 I think, speak, and move at my usual rate of speed.
    1 I find that my thinking is slowed down or my voice sounds dull or flat.
    2 It takes me several seconds to respond to most questions and I'm sure my thinking is slowed.
    3 I am often unable to respond to questions without extreme effort.

16. Feeling restless:

    0 I do not feel restless.
    1 I'm often fidgety, wringing my hands, or need to shift how I am sitting.
    2 I have impulses to move about and am quite restless.
    3 At times, I am unable to stay seated and need to pace around.

To Score:

1. Enter the highest score on any 1 of the 4 sleep items (1-4) _____
2. Item 5 _____
3. Enter the highest score on any 1 appetite/ weight item (6-9) _____
4. Item 10 _____
5. Item 11 _____
6. Item 12 _____
7. Item 13 _____
8. Item 14 _____
9. Enter the highest score on either of the 2 psychomotor items (15 and 16) _____

TOTAL SCORE (Range 0-27) _____

Appendix 8 Work Productivity and Activity Impairment Questionnaire: Psoriasis V2.0 (WPAI:PSO)

The following questions ask about the effect of your psoriasis on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your psoriasis? *Include hours you missed on sick days, times you went in late, left early, etc., because of your psoriasis. Do not include time you missed to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your psoriasis affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If psoriasis affected your work only a little, choose a low number. Choose a high number if psoriasis affected your work a great deal.

Consider only how much psoriasis affected productivity while you were working.

Psoriasis had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Psoriasis completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your psoriasis affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If psoriasis affected your activities only a little, choose a low number. Choose a high number if psoriasis affected your activities a great deal.

Consider only how much psoriasis affected your ability to do your regular daily activities, other than work at a job.

Psoriasis had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Psoriasis completely prevented me from doing my daily activities

CIRCLE A NUMBER

WPAI:PSO V2.0 – English (US)

Appendix 9 Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 Published: 28 May 2009 (v4.03: 14 June 2010)

Investigations (page 42):

Investigations					
	Grade				
Adverse Event	1	2	3	4	5
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9 /L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of lymphocytes in a blood specimen.					

Diarrhea (page 13):

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by frequent and watery bowel movements.					

Appendix 10 Bristol Stool Chart