A PHASE 2, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED, STUDY TO EVALUATE THE SAFETY AND EFFICACY OF PF-06826647 IN PARTICIPANTS WITH MODERATE TO SEVERE PLAQUE PSORIASIS

Investigational Product Number:	PF-06826647
Investigational Product Name:	Not Available (N/A)
United States (US) Investigational New Drug (IND) Number:	CCI
European Clinical Trials Database (EudraCT) Number:	2018-004669-16
Protocol Number:	C2501004
Phase:	2b

Protocol Amendment Summary of Changes Table

Document	Version Date	Summary of Changes and Rationale
Amendment 1	01 October 2019	1. Amendment 1 has become necessary to update the contraception language and to align with emerging development of program safety requirements (protocol C2501003 for ulcerative colitis). Rationale: the purpose of the update is to mitigate a theoretical risk of CYP3A induction by PF-06826647 and thereby potentially lowering the efficacy of hormonal contraceptives. Given the potential teratogenicity risk of PF-06826647, the addition of a barrier method for female participants on hormonal contraception is included. Since the expected maximum change in exposure based on fraction metabolized [f_m] value is approximately 2-fold, the ethinylestradiol containing contraceptives are now allowed. See Section 4.3, 5.3.1 & Appendix 10.4.2 and 10.4.4 for details. 2. Removed body mass index (BMI) see Section 5.1 Inclusion Criteria #6. Rationale: It does not impact PK or PD. 3. Added two exclusion criteria see Section 5.2 Exclusion Criteria: #13. History of recurrent (≥2) venous thrombosis or any arterial thromboembolism or known blood clotting disorders. #14. History of acute coronary syndrome (eg, myocardial infarction, unstable angina pectoris) and any history of cerebrovascular disease within 24 weeks before screening. Rational: to clarify and provide more

		specific language on the criteria. 4. Added language to Discontinuation of Study Intervention involving thromboembolic events see Section 7.1. Rationale: to provide consistency across the program. 5. Added language to Safety Adjudication Committee Section 9.5.2. Rational: to align with program language to specifically include events requiring adjudication are cardiovascular events including venous thromboembolic events (VTE). 6. The content of five Protocol Administrative Clarification Letters (PACLs) # 1-5 was added. • PACL 1: 1) HIV serology should also include Hep B tests as described in EC #21. 2) Appendix 2 should include the above. 3) PROs should be completed in a certain same order (pre and post Day 15). Rationale: to ensure consistency throughout protocol. • PACL 2: typographical error of absolute lymph count (should be 1000 not 800). Rationale: clarification. • PACL 3 JAPAN Only: EC #23 clarified subjects will have HBV DNA testing if there is no documentation of HBV vaccination. Rationale: country requirement. • PACL 4: Concomitant medications guselkumab and risankizumab were added to the agents requiring 6-month

		washout. Rationale: frequently asked question by Investigators regarding new therapeutics. • PACL 5: 1) C-SSRS footnote to clarify the use of "Lifetime" version at baseline. 2) PRO footnote to clarify pre-dose to be consistent with other sections. 3) discrepancy clarified that no live vaccines allowed 8 weeks after last dose. 4) Justification for Dose section 4.3 discrepancy corrected to confirm 83% not 82%. Rationale: to ensure consistency throughout protocol. • Additional discrepancies were eliminated, and typographical errors corrected.
Original protocol	14 December 2018	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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1. PROTOCOL SUMMARY

1.1. Synopsis

Rationale: This multicenter study is being conducted to provide additional PF-06826647 safety and tolerability data, and to further explore the clinical efficacy of PF-06826647 in the treatment of moderate to severe plaque psoriasis. Additionally, the study is intended to enable selection of oral dose and dosing regimen for the future clinical development of PF-06826647.

Objectives, Endpoints, and Estimands:

Investigational Treatment Period:

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
To compare the efficacy of multiple dose levels of PF-06826647 versus placebo on the proportion of participants with moderate to severe plaque psoriasis achieving PASI 90.	• Proportion of participants achieving PASI 90 (90% or greater improvement from Baseline) at Week 16.	Estimand E1: This estimand is intended to provide a population level estimate of the treatment effect of the IP alone on a binary responder endpoint; without the benefit of additional prohibited medications, regardless of participants compliance with the IP dosing. Population: Participants with moderate to severe plaque psoriasis as defined by the inclusion and exclusion criteria without the benefit of additional prohibited medication regardless of compliance. Intercurrent Events: A) Prohibited medication –response will be considered negative for participants after receiving prohibited medication. B) Withdrawal and all other events leading to missing data will be treated as in A. C) Inadequate compliance – participants data will be used as recorded. Population level summary: The difference in proportions between treated and placebo response rates.

Secondary:	**Secondary:**	**Secondary:**
To compare the efficacy of multiple dose levels of PF-06826647 versus placebo on the proportion of participants with moderate to severe plaque psoriasis achieving PASI 75.	Key secondary endpoint: • Proportion of participants achieving PASI 75 (75% or greater improvement from Baseline) at time points specified in the Schedule of Activities (SoA).	The binary secondary endpoints, when appropriate, will be analyzed descriptively and using estimand E1.
To compare the efficacy of multiple dose levels of PF-06826647 versus placebo on PGA score in participants with moderate to severe plaque psoriasis.	• Proportion of participants with PGA score clear (0) or almost clear (1) and ≥2 points improvement from baseline at time points specified in the SoA. • Proportion of participants with PGA score clear (0) or almost clear (1) at time points specified in the SoA.	
To compare the efficacy of multiple dose levels of PF-06826647 versus placebo on the proportion of participants with moderate to severe plaque psoriasis achieving PASI 50 and PASI 100.	• Proportion of participants achieving PASI 50 (50% or greater improvement from Baseline), PASI 100 (100% from Baseline) at time points specified in the SoA.	
To compare the efficacy of multiple dose levels of PF-06826647 versus placebo on PGA and PASI scores in participants with moderate to severe plaque psoriasis.	• Change from baseline and percent change from baseline in PASI scores at time points specified in the SoA.	Estimand E2: This estimand is intended to provide a population level estimate of the treatment effect of the IP alone on a continuous endpoint; without the benefit of additional prohibited medications, regardless of participants compliance with the IP dosing. Population: Participants with moderate to severe plaque psoriasis as defined by the inclusion and exclusion criteria without the benefit of additional prohibited medications regardless of compliance. Intercurrent Events: A) Prohibited medication – all scores after participants receive prohibited
To compare the effect of multiple dose levels of PF-06822647 versus placebo in Peak-Pruritus Numerical Rating Scale score in participants with moderate to severe plaque psoriasis.	• Absolute score and change from baseline in Peak-Pruritus Numerical Rating Scale score at time points specified in the SoA.	

		medication will be omitted from the analysis and treated as missing scores. Missing scores will be imputed based on the assumption that participants do not benefit from the IP treatment. B) Withdrawal and all other events leading to missing data will be treated similarly as in A. C) Inadequate compliance – participants data will be used as recorded. Population level summary: The mean difference between treated and placebo arms of the change from baseline PASI score. All continuous endpoint, when appropriate will be analyzed descriptively and using estimand E2 described above when appropriate.
To assess the safety and tolerability of PF-06826647 in participants with moderate to severe plaque psoriasis.	• Incidence and severity of adverse events, serious adverse events and withdrawals due to adverse events. • Change from baseline in clinical laboratory values (chemistry and hematology, lipids). • Incidence of clinically significant changes in ECG (heart rate, QT, QTc, PR and QRS intervals). • Change from baseline in vital signs (blood pressure, pulse rate and temperature measurements).	There is no defined estimand for these endpoints and they will be analyzed using Pfizer data standards as applicable.
To compare the efficacy of multiple dose levels PF-06826647 versus placebo on measures of disease and symptom severity in participants with moderate to severe plaque psoriasis.	• Absolute score and change from baseline Psoriasis Symptom Inventory at time points specified in the SoA.	These endpoints will be analyzed descriptively and using estimand E2 described above when appropriate.

Extension Treatment Period:

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
To assess the safety and tolerability of PF-06826647 in participants with moderate to severe plaque psoriasis.	• Incidence and severity of adverse events, serious adverse events and withdrawals due to adverse events. • Change from baseline in clinical laboratory values (chemistry, hematology & lipids). • Incidence of clinically significant changes in ECG (heart rate, QT, QTc, PR and QRS intervals). • Change from baseline in vital signs (blood pressure, pulse rate and temperature measurements).	Not Applicable-will be analyzed descriptively and according to the Pfizer standard.

Overall Design:

This is a Phase 2b, randomized, double blind, placebo controlled, and multicenter study in participants with moderate to severe plaque psoriasis. Following a Screening period of up to 6 weeks, is a 16 week placebo controlled Investigational Treatment Period with double blind oral daily treatment using the following doses: 50 mg, 100 mg, 200 mg, 400 mg. All participants completing the 16 week Investigational Period may continue on to a 24 week non-placebo controlled Extension Treatment Period with double blind oral daily treatment, if per the Investigator judgment the participant is compliant with study procedures and continued participation presents no safety risks. The participants continuing into the Extension Treatment Period that were originally randomized to the 200 mg and 400 mg treatment groups will continue on their respective doses, while those randomized to one of the other treatment groups (including placebo) will be randomly assigned (at study baseline) to receive either 200 mg or 400 mg during the Extension Treatment Period. The total duration of study participation will be approximately 50 weeks, including up to 6 weeks Screening, 16 week Investigational Treatment Period, 24 week Extension Treatment Period and a Follow-Up visit 4 weeks after the Extension Period ends.

Number of Participants:

Approximately 160 participants (40 participants in each of the following arms: placebo, 200 mg, and 400 mg; and 20 participants in each of the following arms: 50 mg and 100 mg) will be randomly assigned to a treatment group in order to ensure a minimum of 128 evaluable participants completing Week 16 (assuming a 20% dropout rate).

Intervention Groups and Duration:

During the Investigational Treatment Period (Weeks 0 through 16), the 160 participants will receive PF-06826647 (50 mg, 100 mg, 200 mg, 400 mg) once daily, or matching placebo and the same participants will continue onto the Extension Treatment Period.

After completion of the 16 week placebo controlled Investigational Study Period, participants may transition directly into the 24 week Extension Study Period.

The total duration of study participation will be approximately 50 weeks, including up to 6 weeks Screening, 16 week Investigational Treatment Period, the 24 week Extension Treatment Period and a Follow-Up visit 4 weeks after the Extension Period ends.

Data Monitoring Committee:

This study will use an internal review committee (IRC) (Section 9.5.1).

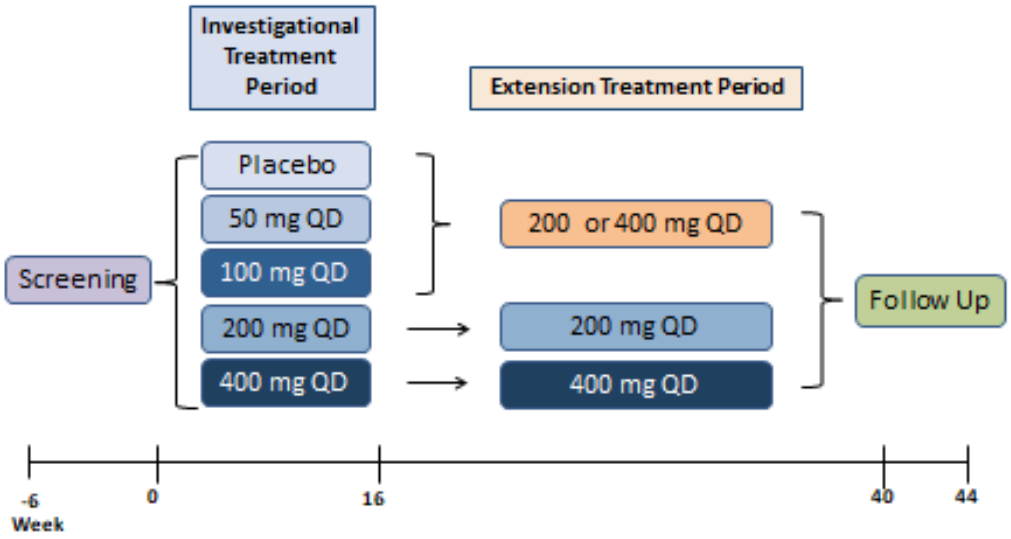
Statistical Methods:

The primary estimand will be the population average treatment effect on PASI 90 rates at Week 16 relative to placebo without regard to compliance in the absence of prohibited medication.

The analysis of the primary estimand will be of the proportion of participants achieving: PASI 75 (75% or greater improvement from Baseline); PGA score clear (0) or almost clear (1) and ≥2 points improvement from baseline; PGA score clear (0) or almost clear (1); PASI 50 (50% or greater improvement from Baseline) and PASI 100 (100% or greater improvement from Baseline). The analysis of the secondary estimand will be of the change from baseline and percent change from baseline in PASI scores; and absolute score and change from baseline in Peak-Pruritus Numerical Rating Scale score.

All other key secondary continuous clinical endpoints will be analyzed using the secondary estimand, while all other key secondary categorical clinical endpoints will be analyzed using the primary estimand.

1.2. Schema


Investigational Treatment Period
Extension Treatment Period
Placebo
50 mg QD
100 mg QD
200 mg QD
400 mg QD
Screening
200 or 400 mg QD
200 mg QD
400 mg QD
Follow Up
-6
Week
0
16
40
44

1.3. Schedule of Activities (SoA)

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant

Study Procedure	**Screening**	**Baseline**	**Investigational Treatment Period**							**Extension Treatment Period**		**Follow-Up[b]**	**Early Termination[c]**
Visit Identifier (Week)	**-6 to -1**	**0**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**18/20/24/28/32/36**	**40**	**20 or 44**	
Study Day[a]	**-42 to -1**	**1**	**8**	**15**	**29**	**43**	**57**	**85**	**113**	**127/141/169/197/225/253**	**281**	**141 or 309**	
Visit Window (Days)	**N/A**		**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	
Enrollment Procedures													
Informed consent	X												
Medical history & demography	X												
Eligibility assessment	X	X											
Medication History	X												
Randomization		X											
Clinical Assessments													
Full Physical Exam	X	X							X		X		X
Brief Physical Exam			X	X	X	X	X	X		X		X	
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG[d]	X	X			X				X		X		X
Height/Weight[e]	X	X							X		X		
Chest radiograph[f]	X												
C-SSRS[g]	X	X							X		X		
Laboratory Assessments													
Hematology/Blood chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X
Lipid panel[h] (fasting)		X			X				X		X		
Urinalysis[i]	X	X			X				X		X		
FSH[j]	X												
Serum β-HCG[k]	X												

Study Procedure	Screening	Baseline	Investigational Treatment Period							Extension Treatment Period		Follow-Up[b]	Early Termination[c]
Visit Identifier (Week)	**-6 to -1**	**0**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**18/20/24/28/32/36**	**40**	**20 or 44**	
Study Day[a]	**-42 to -1**	**1**	**8**	**15**	**29**	**43**	**57**	**85**	**113**	**127/141/169/197/225/253**	**281**	**141 or 309**	
Visit Window (Days)	**N/A**		**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	
Urine β-HCG[l] (done at site)		X	X	X	X	X	X	X	X	X	X	X	X
HIV serology/HBsAg, HBcAb, (HepB reflex testing), and HCVAb[m]	X												
Tuberculosis test[n]	X												
CCI													
CCI													
Study treatment													
IP dispensing[q]		X	X	X	X	X	X	X	X	X			
IP accountability			X	X	X	X	X	X	X	X	X		X
Dosing diary[r]			X	X	X	X	X	X	X	X	X		X
Clinical Assessments of psoriasis													
PASI, CCI PGA	X	X	X	X	X	X	X	X	X	X	X	X	X
PROs[s]													
Psoriasis Symptom Inventory		X	X	X	X		X	X	X	X[t]	X	X	X
PP-NRS		X	X	X	X		X	X	X	X[t]	X	X	X
										C			
										C			
										I			

Study Procedure	Screening	Baseline	Investigational Treatment Period							Extension Treatment Period		Follow-Up[b]	Early Termination[c]
Visit Identifier (Week)	**-6 to -1**	**0**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**18/20/24/28/32/36**	**40**	**20 or 44**	
Study Day[a]	**-42 to -1**	**1**	**8**	**15**	**29**	**43**	**57**	**85**	**113**	**127/141/169/197/225/253**	**281**	**141 or 309**	
Visit Window (Days)	**N/A**		**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	
[redacted]													
Monitoring													
Contraception Check[v]		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Treatment(s)		X	X	X	X	X	X	X	X	X	X	X	X
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE= adverse event; [redacted] C-SSRS= Columbia Suicide Severity Rating Scale; [redacted] ECG = electrocardiogram; [redacted] FSH= follicle stimulating hormone; HBsAg= hepatitis B surface antigen; HBcAb= hepatitis B core antibody; HCVAb= hepatitis C virus antibody; β-HCG= human chorionic gonadotropin; HIV= human immunodeficiency virus; IP = Investigational Product; PASI = Psoriasis Area and Severity Index; PP-NRS= Peak-Pruritus Numerical Rating Scale PE= physical exam; PGA= Physician's Global Assessment; PRO = patient reported outcome; WOCBP= women of child-bearing potential.

a. Days relative to Day 1.

b. Perform Follow-Up visit to the Investigational Treatment Period at Week 20 only if the participant does not continue into the Extension Treatment Period. Otherwise Follow-Up is completed at Week 44.

c. Participants who prematurely withdraw during Investigational Treatment Period or during the Extension Treatment Period should return for an Early Termination (ET) visit occurring 1 week after their last dose whenever possible and continue visits per Investigator's discretion until the event has returned to normal or baseline levels or is deemed clinically stable.

d. 12-lead locally read singlicate ECG should be performed after the participant has rested quietly for at least 10 minutes and before laboratory blood collection. Vital signs consist of blood pressure, pulse rate, and temperature and should be performed before laboratory blood collection and after 5 minutes rest while preferably sitting (supine is allowed). Participants should not smoke or ingest caffeine 30 minutes prior to blood pressure and pulse rate measurements.

e. Height only measured at Screening; height and weight will be measured without shoes.

f. Chest X-ray or other appropriate chest diagnostic imaging (ie, CT or MRI) may be performed within 12 weeks prior to Day 1.

g. Use C-SSRS "Lifetime" version at Screening and Baseline and "Since Last Visit" version at visits indicated in SoA. Participants who have recent or active suicidal ideation or behaviors will be excluded from study entry or after Day 1, would be discontinued from treatment and referred to a mental health professional for appropriate evaluation and treatment.

h. Participants must be fasting (water only) for at least 8 hours prior to visits, when lipid panel is being assessed.

i. Dipstick in all cases; microscopy analysis is indicated if urinalysis is positive for blood, nitrite, leukocyte esterase and/or protein. Urine culture is performed if urinalysis is positive for nitrite and/or leukocyte esterase or if clinically indicated.

j. To be done in females (<60 years of age) who are amenorrheic for at least 12 consecutive months.

k. Required for WOCBP at Screening

l. Required for WOCBP prior to dosing at baseline and at all subsequent visits. To be conducted at the site. Pregnancy tests (serum or urine) may also be repeated more frequently as per request of IRBs/ECs or if required by local regulations.

m. HepB reflex testing only if HBsAg negative but HBcAb positive at Screening. If result of HCVAb is positive, or if Hepatitis C Virus (HCV) antibody result is indeterminate, then a HCV RNA AMPLIPREP TAQMAN 2.0 will automatically be performed. In Japan see Section 5.1 for HBV and HCV details.

n. If not performed within 12 weeks prior to Screening (see Assessments Section 8.2.1.1 for details).

o. PK samples will be collected per SoA prior to dosing, and at 0.5 hour (±5 min); at 1 and 2 hours (±10 min) and 4 hours (±20 min) post dose hours.

C [redacted]

q. Participants should take blinded study medication daily during the Investigational Treatment Period and Extension Period; however, on study visit days, participants are instructed to refrain from dosing at home, and are to take the dose in the clinic.

r. Participants will be reminded to complete the dosing diary daily throughout the study.

s. All procedures should be performed before dosing of IP. Effort should be made to complete all PRO questionnaires before any other assessments except at Baseline when eligibility needs to be confirmed.

t. Psoriasis Symptom Inventory, Peak-Pruritus Numerical Rating Scale CCI [redacted] scales to be completed daily for the first two weeks pre -dose as per SoA and at visits Weeks 4, 8, 12, 16, 24, 36 and Follow-up.

C [redacted]
C

v. To confirm that contraception, if assigned, is used consistently and correctly.

2. INTRODUCTION

PF-06826647 is a potent tyrosine kinase 2 (TYK2) inhibitor with a favorable selectivity profile over other human kinases and is being investigated in participants with plaque psoriasis. Based on its cytokine inhibition profile, PF-06826647 is expected to target the T-helper 1 (Th1), T-helper 17 (Th17), and Types I interferon signaling pathways directly by inhibiting TYK2. This should provide therapeutic benefit in the treatment of inflammatory conditions driven by Th1/Th17 and interferon immune responses.

2.1. Study Rationale

The purpose of this multicenter, placebo controlled double blind study is to provide additional efficacy, safety, tolerability CCI data regarding PF-06826647 in the oral treatment of moderate to severe plaque psoriasis. It is intended to enable dose selection for the future development of PF-06826647.

2.2. Background

The most common variant of psoriasis or plaque psoriasis, is a chronic inflammatory autoimmune skin disease characterized by red, scaly, raised plaques. Chronic plaque psoriasis is a common skin disorder with a worldwide prevalence of 2% and afflicts an estimated 7.4 million Americans. Although psoriasis primarily affects the skin and is not a life threatening disease, it can profoundly impact the patient's quality of life (QoL) resulting in impairment akin to other major diseases, such as diabetes, cardiovascular disease, and psoriatic arthritis.[1]

The Janus kinase (JAK) family, which includes JAK1, JAK2, JAK3 and TYK2, is a group of cytoplasmic tyrosine kinases that mediate signal transduction via interactions with Type 1 and Type 2 cytokine receptors critical for immune cell function, survival, activation, and proliferation.[2] TYK2 pairs with JAK1 to mediate type I interferon (IFN) signaling and with JAK2 to transmit interleukin (IL) IL-12 and IL-23 signaling. Both of these key cytokines are implicated in the pathophysiology of plaque psoriasis. IL-12 and IL-23 require TYK2 for signal transduction,[3] indicating that inhibition of TYK2 mediated signaling could be efficacious in the treatment of these inflammatory conditions.

Over activation of Th17 and the main effector cytokines of Th17 cells has been linked to various inflammatory diseases, including psoriasis.[4] Th17 cells are elevated in psoriatic lesions, along with levels of proinflammatory cytokines, including IL-17A, IL-17F, IL-17C, which are expressed by Th17 cells and are likely mediators of inflammation and tissue damage.[5] Human genetic studies implicate the Th17 pathway in psoriasis, and have uncovered likely risk alleles which include genes involved in IL-23 signaling and genes that function downstream of the IL-17 receptor.[6] In addition to genetic evidence, several effective psoriasis therapies target Th17 cytokine production, suggesting a central role of Th17 and IL-17 in the disease. The newest and most effective therapeutics are directed to the cytokines and cytokine signaling of interleukin-23/type 17 T cell (IL-23/T17) axis.[7] Additionally, the TYK2-selective inhibitor, BMS-986165, recently showed efficacy in a Phase 2 psoriasis study.[8] Thus, there is strong rationale for targeting the Th17 pathway in the treatment of psoriasis.

2.2.1. Non-Clinical Safety Studies with PF-06826647

No adverse findings were observed in oral repeat dose toxicity studies with PF-06826647 in rats and monkeys up to 6 and 9 months in duration, respectively. Test article related, nonadverse, target organs identified include the immune and hemolymphatic systems (thymus, spleen, lymph nodes, bone marrow, erythron, and leukon), liver (increased transaminases), and bone (increased trabecular thickness). The findings in the immune and hemolymphatic systems are consistent with the pharmacological activity of PF-06826647. In the 6-month toxicity study in rats, the no-observed-adverse-effect level (NOAEL) was 500 mg/kg/day (250 mg/kg BID) with unbound and total maximum concentration C_{max} values of 1680 and 9360 ng/mL, respectively, and unbound and total AUC_{24} (area under the curve 24 hours) values of 16,600 and 92,000 ng•h/mL, respectively. In the 9-month toxicity study in monkeys, the NOAEL was 220 mg/kg/day with unbound and total C_{max} values of 663 and 1950 ng/mL, respectively, and unbound and total AUC_{24} values of 8130 and 23,900 ng•h/mL, respectively. In an embryo fetal development study in rabbits, adverse PF-06826647-related embryolethality due to higher incidence of late resorptions resulting in higher postimplantation loss and lower number of live fetuses was observed at 500 mg/kg/day (unbound C_{max} of 1290 ng/mL and AUC_{24} of 17,300 ng•h/mL). The developmental NOAEL in rats was 500 mg/kg/day (unbound C_{max} of 1850 ng/mL and AUC_{24} of 19,600 ng•h/mL), and in rabbits was 150 mg/kg/day (unbound C_{max} of 864 ng/mL and AUC_{24} of 9930 ng•h/mL). PF-06826647 was not mutagenic in bacterial reverse mutation assays. Although PF-06826647 was positive for micronuclei formation in vitro (through an aneugenic mechanism), it did not induce micronuclei in vivo in rats at 500 mg/kg/day (250 mg/kg BID) (unbound C_{max} of 2110 ng/mL and AUC_{24} of 24,100 ng•h/mL), the highest dose tested in the 1-month study. No evidence of PF-06826647 related phototoxicity in the skin or eyes of pigmented rats in a 3-day phototoxicity study was observed up to the highest dose tested of 500 mg/kg/day, demonstrating that PF-06826647 was not a phototoxicant, in vivo.

Further details of the nonclinical safety program are provided in the current investigator's brochure.

2.2.2. Non-Clinical Pharmacokinetics and Metabolism

Single dose pharmacokinetic studies with PF-06826647 were conducted after oral and intravenous (IV) administration to mice and rats. PF-06826647 had moderate oral bioavailability (26% to 51%) utilizing a sprayed-dried dispersion (SDD) formulation versus 0.5% methyl cellulose (<1% to 12%). After IV administration, PF-06826647 demonstrated a steady state volume of distribution (Vss) of approximately 0.9 to 1.4 L/kg and a low plasma clearance (CL [10 to 18 mL/min/kg]), relative to mouse and rat liver blood flows. Systemic exposures (maximum observed concentrations [C_{max}] and area under the concentration time curve [AUC]) of PF-06826647 after repeat oral dosing in the pivotal toxicity studies increased with increasing dose in rats (up to 500 mg/kg/day) and monkeys (up to 300 mg/kg/day) in a less than dose-proportional manner. No sex-related differences in exposure and no accumulation of PF-06826647 were observed over the dosing period in either species. In vitro, PF-06826647 showed high apparent passive permeability and may be a substrate for P-glycoprotein (P-gp). PF-06826647 binding to plasma proteins ranged

between 62% to 82%, and PF-06826647 does not preferentially partition into red blood cells from nonclinical species and humans.

Renal and biliary excretion of PF-06826647 was limited in the rat. No unique human metabolites were observed in vitro compared to metabolite profiles in rat and monkey. The major human clearance pathway for PF-06826647 is expected to be hepatic cytochrome P450 (CYP)-mediated metabolism by CYP1A2 (fraction metabolized [f_m] = 0.53), CYP2D6 (f_m = 0.26) and CYP3A (f_m = 0.21). PF-06826647 did not inhibit the major cytochrome CYP450 or UDP- glucuronosyltransferase enzymes (UGT) (half maximal inhibitory concentration IC_{50} >25 µM). PF-06826647 induced CYP3A4 messenger Ribonucleic acid (mRNA) expression in 1 of 3 lots of hepatocytes (≥4.7-fold increase at ≥10 µM), but no corresponding induction was seen in CYP3A4 enzymatic activity. Induction of CYP1A2 enzyme activity occurred in 2 lots of hepatocytes (approximately 2-fold at ≥10 µM), and PF-06826647 did not induce CYP2B6 mRNA levels or enzymatic activity. Based on its in vitro profile, the potential for PF-06826647 mediated CYP450 or UGT drug interactions is low at clinically relevant concentrations (C_{max} 355 nM; $C_{max,u}$ 135 nM).

PF-06826647 showed little to no inhibition of the multidrug and toxin extrusion protein (MATE1), multidrug resistant protein 1 (MDR1), multidrug resistance-associated protein (MRP2), MRP3, sodium/taurocholate co-transporting polypeptide (NTCP), organic anion transporting polypeptide (OATP) 1B1, OATP1B3 and organic cation transporter (OCT) 2. However, PF-06826647 did inhibit MATE2K with an estimated IC_{50} value of 0.53 µM.

2.2.3. Clinical Overview

The clinical development program for PF-06826647 is currently comprised of a placebo-controlled Phase 1 study (C2501001). In this study, six Single Ascending Dose (SAD) cohorts and five Multiple Ascending Dose (MAD) cohorts in healthy participants completed, with 69 healthy adult participants randomized and treated with PF-06826647 or placebo. The study also included one cohort of 6 healthy Japanese participants who received 400 mg once daily (QD) and 2 cohorts of participants (total 40) with moderate to severe plaque psoriasis (First-in-Patient) who received 400 mg or 100 mg QD of PF-06826647 or placebo. Psoriasis participants received active treatment with PF-06826647 (100 mg or 400 mg QD for 28 days) had clinically meaningful decreases in disease activity as measured by Psoriasis Area and Severity Index (PASI), the defined primary endpoint.

Safety, efficacy, CCI [redacted] results from this study support further development of PF-06826647 in plaque psoriasis. The Phase 1 study (C2501001) demonstrated an acceptable safety and pharmacokinetic profile at single doses of PF-06826647 ranging from 3 mg to 1600 mg in the SAD portion and ten-day dosing from 10 mg to 1200 mg daily in the MAD portion of the study. Dose escalation stopping rules were not triggered. There were no clinically meaningful findings in vital signs, electrocardiograms (ECG), or potential Hy's Law cases reported during this study. In addition, there were no serious adverse events (including death) or Suspected, Unexpected, Serious Adverse Reactions (SUSARs) reported. Based on preliminary review of treatment group data, all reported treatment emergent adverse events have been of mild intensity.

Additionally, clinical benefit was observed in participant cohorts with plaque psoriasis as measured by the change from baseline in PASI scores over a 28-day treatment period. In the participants completing 28 days of treatment with PF-06826647, the mean placebo-adjusted change from baseline PASI score at Week 4 was -14.02 (n=20) for the 400 mg QD cohort and -4.55 (n=15) for the 100 mg QD cohort.

Please refer to Benefit/Risk Assessment Section 2.3 for more details on the clinical safety of PF-06826647.

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2.3. Benefit/Risk Assessment

PF-06826647 is expected to offer therapeutic benefit in the treatment of psoriasis. More specifically, inhibition of IL-12 and IL-23 signaling mediated by TYK2 inhibitory activity may provide a new and improved therapeutic benefit due to potential achievement of disease control, improvement of signs and symptoms, as well as improvements in quality of life.

Overall, the safety profile observed during the Phase 1 program for PF-06826647 appears to be acceptable at dosages up to 1200 mg daily administered orally over 10 days. A longer dosing duration was explored in participants with moderate to severe psoriasis, who received the maximum PF-06826647 dose level of 400 mg and 100 mg daily for 28 days. No serious or severe AEs were reported in the Phase 1 study. There was one psoriasis participant in the 400 mg cohort who met the protocol pre-specified stopping criteria due to decreased level of lymphocytes, although this participant had borderline low lymphocytes at baseline. As with other immunomodulators, the risk of infection is a potential concern due to the immunosuppressive effects of PF-06826647.

In conclusion, the sponsor considers that the available information from the nonclinical and clinical data to date regarding PF-06826647 provide a favorable benefit-risk profile and supports its continued investigation as a potential treatment for plaque psoriasis.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of PF-06826647 may be found in the investigator's brochure, which is the single reference safety document (SRSD) for this study.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

3.1. Study Objectives, Endpoints and Estimands -- Investigational Treatment Period

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
To compare the efficacy of multiple dose levels of PF-06826647 versus placebo on the proportion of participants with moderate to severe plaque psoriasis achieving PASI 90.	• Proportion of participants achieving PASI 90 (90% or greater improvement from Baseline) at Week 16.	Estimand E1: This estimand is intended to provide a population level estimate of the treatment effect of the IP alone on a binary responder endpoint; without the benefit of additional prohibited medications, regardless of participant's compliance with the IP dosing. Population: Participants with moderate to severe plaque psoriasis as defined by the inclusion and exclusion criteria without the benefit of additional prohibited medication regardless of compliance. Intercurrent Events: A) Prohibited medication –response will be considered negative for participants after receiving prohibited medication. B) Withdrawal and all other events leading to missing data will be treated as in A). C) Inadequate compliance – participants data will be used as recorded. Population level summary: The difference in proportions between treated and placebo response rates.
Secondary:	**Secondary:**	**Secondary:**
To compare the efficacy of multiple dose levels of PF-06826647 versus placebo on the proportion of participants with moderate to severe plaque psoriasis achieving PASI 75.	Key secondary endpoint: • Proportion of participants achieving PASI 75 (75% or greater improvement from Baseline) at time points specified in the Schedule of Activities (SoA).	The binary secondary endpoints, when appropriate, will be analyzed descriptively and using estimand E1.
To compare the efficacy of multiple dose levels of PF-06826647 versus placebo on PGA score in participants	• Proportion of participants with PGA score clear (0) or	

with moderate to severe plaque psoriasis.	almost clear (1) and ≥2 points improvement from baseline at time points specified in the SoA. • Proportion of participants with PGA score clear (0) or almost clear (1) at time points specified in the SoA.	
To compare the efficacy of multiple dose levels of PF-06826647 versus placebo on the proportion of participants with moderate to severe plaque psoriasis achieving PASI 50 and PASI 100.	• Proportion of participants achieving PASI 50 (50% or greater improvement from Baseline), PASI 100 (100% from Baseline) at time points specified in the SoA.	
To compare the efficacy of multiple dose levels of PF-06826647 versus placebo on PGA and PASI scores in participants with moderate to severe plaque psoriasis.	• Change from baseline and percent change from baseline in PASI scores at time points specified in the SoA.	Estimand E2: This estimand is intended to provide a population level estimate of the treatment effect of the IP alone on a continuous endpoint; without the benefit of additional prohibited medications, regardless of participant's compliance with the IP dosing. Population: Participants with moderate to severe plaque psoriasis as defined by the inclusion and exclusion without the benefit of additional prohibited medications regardless of compliance. Intercurrent Events: A) Prohibited medication – all scores after participants receive prohibited medication will be omitted from the analysis and treated as missing scores. Missing scores will be imputed based on the assumption that participants do not benefit from the IP treatment. B) Withdrawal and all other events leading to missing data will be treated similarly as in A). C) Inadequate compliance – participants data will be used as recorded.

To compare the effect of multiple dose levels of PF-06822647 versus placebo in Peak-Pruritus Numerical Rating Scale score in participants with moderate to severe plaque psoriasis.	• Absolute score and change from baseline in Peak-Pruritus Numerical Rating Scale score at time points specified in the SoA.	
To assess the safety and tolerability of PF-06826647 in participants with moderate to severe plaque psoriasis.	• Incidence and severity of adverse events, serious adverse events and withdrawals due to adverse events. • Change from baseline in clinical laboratory values (chemistry, hematology & lipids). • Incidence of clinically significant changes in ECG (heart rate, QT, QTc, PR and QRS intervals). • Change from baseline in vital signs (blood pressure, pulse rate and temperature measurements).	There is no defined estimand for these endpoints and they will be analyzed using Pfizer data standards as applicable.
To compare the efficacy of multiple dose levels PF-06826647 versus placebo on measures of disease and symptom severity in participants with moderate to severe plaque psoriasis.	• Absolute score and change from baseline Psoriasis Symptom Inventory at time points specified in the SoA.	This endpoint will be analyzed descriptively and using estimand E2 described above when appropriate.
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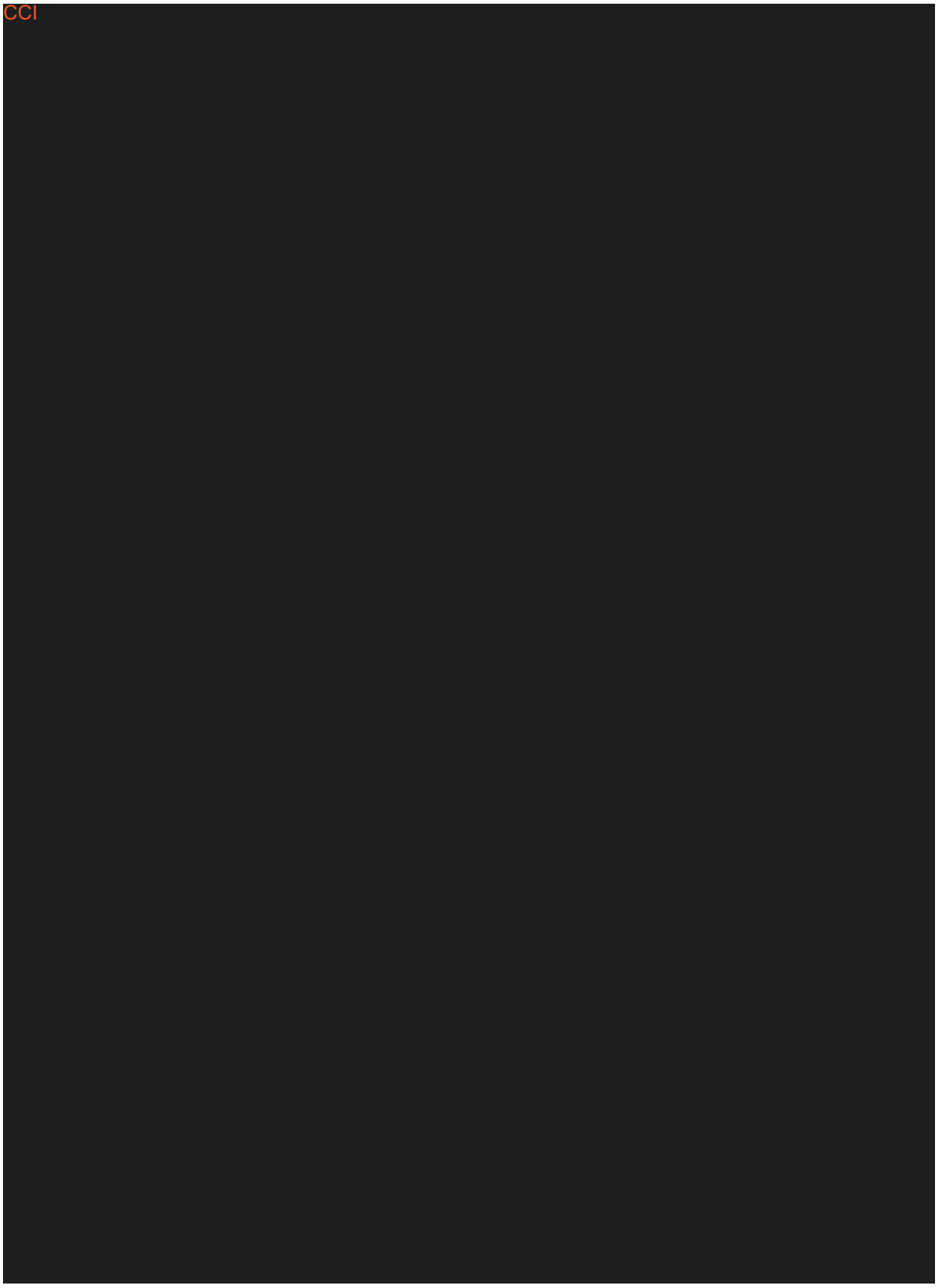

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Study Objectives, Endpoints and Estimands -- Extension Treatment Period

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
To assess the safety and tolerability of PF-06826647 in participants with moderate to severe plaque psoriasis.	• Incidence and severity of adverse events, serious adverse events and withdrawals due to adverse events. • Change from baseline in clinical laboratory values (chemistry, hematology & lipids). • Incidence of clinically significant changes in ECG (heart rate, QT, QTc, PR and QRS intervals). • Change from baseline in vital signs (blood pressure, pulse rate and temperature measurements).	Not Applicable, will be analyzed descriptively and according to the Pfizer standard.

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4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2b, randomized, double blind, placebo controlled, parallel group, multicenter study in participants with moderate to severe plaque psoriasis. After a screening period of - up to 6 weeks, eligible participants will be randomized in a 2:1:1:2:2 ratio such that participants will receive placebo or either one of four PF-06826647 daily dose levels (50 mg, 100 mg, 200 mg or 400 mg) every day during the Investigational Treatment Period for 16 weeks in a blinded fashion. All participants completing the 16-week Investigational Period will continue to a 24-week non-placebo-controlled Extension Treatment Period with double blind oral daily treatment, if per the Investigator judgment the participant is compliant with study procedures and continued participation presents no safety risks. The participants continuing into the Extension Treatment Period that were originally randomized to the

200 mg and 400 mg treatment groups will continue their respective doses, while those randomized to one of the other treatment groups (including placebo) will be randomly assigned (at study baseline) to receive either 200 mg or 400 mg during the Extension Treatment Period. Participants who discontinue prior to Week 16 visit will have an Early Termination visit and will not be eligible for the Extension Period.

Approximately 160 participants (40 participants in each of the following arms: placebo, 200 mg, and 400 mg; and 20 participants in each of the following arms: 50 mg and 100 mg) will be randomly assigned to a treatment group in order to ensure a minimum of 128 evaluable participants completing Week 16 (assuming a 20% dropout rate).

The total duration of study participation will be approximately 50 weeks, including up to 6 weeks Screening Period, 16-week Investigational Treatment Period, the 24-week Extension Treatment Period and a Follow-Up visit 4 weeks after the Extension Treatment Period.

If a participant is withdrawn from investigational product (IP) treatment, the participant will proceed with the Early Termination (ET) and Follow Up visits per Schedule of Activities.

4.2. Scientific Rationale for Study Design

This study is being conducted to provide data on efficacy, safety, tolerability, CCI [redacted] of PF-06826647 in the oral treatment of moderate to severe plaque psoriasis. The chronic toxicology package supports the planned study duration.

The treatment duration of 16 weeks in this Phase 2 study (C2501004) will allow for further exploration of the clinical safety and efficacy that was observed in the 4-week Phase 1 (C2501001) study in a small (n=40) number of psoriasis participants. The PASI 90 score at Week 16 will be assessed as the study's primary endpoint. The 50 mg once daily (QD) PF-06826647 dose will be explored in order to identify the minimal clinically efficacious dose after 16 weeks of treatment. In order to further characterize the dose-response relationship, this study will explore 100 mg, 200 mg and 400 mg for 16 weeks during the Investigational Treatment Period of the study. Based on the exposure-response modeling with the PASI data observed up to Week 4, the projected PASI 90 response rates at 200 mg and 400 mg are 47% and 83% at Week 16 respectively, while 50 mg and 100 mg are expected to provide <15% PASI 90 response rate. For this reason, the 50 mg and 100 mg treatment groups will have a smaller allocation of participants as compared to the other treatment groups. Furthermore, participants randomized to placebo, 50 mg, and 100 mg doses during the Investigational Treatment Period will receive either 200 mg or 400 mg during the Extension Study Period in order to evaluate additional safety, tolerability, and durability of response to PF-06826647 at expected clinically efficacious doses.

Since PF-06826647 is metabolized primarily by CYP1A2, CYP3A4 and CYP2D6, the strong and moderate inducers and inhibitors of these drug metabolizing enzymes are prohibited. Dofetilide being a MATE substrate is also prohibited because PF-06826647 is a MATE2K substrate and can potentially increase exposure.

The requirement for female participants using hormonal contraceptives to use an additional barrier method may be removed if supported by the outcome of an ongoing oral contraceptive PK interaction study (Study C2501005).

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Patient reported outcomes will evaluate changes in psoriasis symptoms and health-related quality of life. These utility scores will be further utilized for development of an early cost-effectiveness model.

The potential risk of exposure to PF-06826647 in a sexual partner of a male participant in this study via ejaculate is low, and therefore no barrier contraception (condom) use in male participants is warranted. The calculated safety margin is ≥100-fold between the estimated partner exposure due to seminal transfer and the no-observed-adverse-effect level (NOAEL) for serious manifestations of developmental toxicity in nonclinical studies. The safety margin of 100-fold is based on applying a 10-fold safety factor for interspecies extrapolation and a 10-fold safety factor for susceptible populations.

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4.3. Justification for Dose

Dose selection for this study was based on expected average inhibition of IL-12, IL-23, and IFNα as well as projected in vivo efficacy observed in psoriasis participants without significant JAK2 inhibition. Four dosing (50 mg QD, 100 mg QD, 200 mg QD and 400 mg QD) regimens of PF-06826647 and placebo were selected to explore the dose range in moderate to severe psoriasis participants given the practical considerations.

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Based on the exposure-response modeling with the PASI data observed up to Week 4, the projected PASI 90 response rates of 50 mg, 100 mg, 200 mg, and 400 mg were 3%, 13%, 47%, and 83% at Week 16, respectively. However, there is uncertainty in the extrapolation of response from Week 4 to Week 16. Although the projected PASI 90 response rates of 50 mg QD is low, the projected average inhibition (Table 3) based on in vitro IC_{50} value determined by phosphorylated signal transducer and activator of transcription (pSTAT) modulation in human whole blood, red blood cell (RBC) partition ratio of 1.4 and assuming Hill coefficient of 1, the average daily inhibition of IL-12, IL-23, IFNα is approximately 82%, 69% and 79%, respectively. Considering both the projected PASI 90 response rate and the average inhibition of IL-12 and IL-23, 50 mg was selected as the lowest pharmacologically active dose that would be expected to be clinically minimally efficacious. The highest dose of 400 mg QD was selected based on practical considerations of daily tablet burden to participants and projected high degree of inhibition (>90%) of IL-12, IL-23 and IFNα (Table 3) at steady state.

Additionally, based on data observed to date in both healthy and psoriasis participants, these doses are expected to be safe and well tolerated. All the adverse events (AEs) observed in healthy participants up to 1200 mg QD for 10 days and psoriasis participants up to 400 mg QD for 28 days were mild in nature. Although, the projected average inhibition of erythropoietin (EPO) (Table 3) was 67% and a transient decrease in reticulocyte was observed in psoriasis participants at 400 mg QD, no clinically meaningful change in hemoglobin was observed at the same dose for 28 days in psoriasis participants. The long-term impact of transient decrease in reticulocytes on hemoglobin is currently unknown.

As shown in the Table 3, highest dose of 400 mg QD at steady state is expected to provide margins of about 2-fold for C_{max} and about 3-fold for AUC relative to the total exposure (NOAEL) in the monkey 9-month chronic toxicity study.

In Study C2501001, the 6β-hydroxycortisol/cortisol ratio in urine was evaluated as a marker of CYP3A induction but there were no differences between PF-06826647 treated versus placebo participants. Thus, the risk of induction of metabolic pathways is considered low.

Ethinylestradiol (EE) containing oral contraceptives (OC) has been shown to increase the exposure of CYP1A2 substrates such as caffeine. Based on in vitro experiments, the major human clearance pathway for PF-06826647 is expected to be hepatic CYP-mediated metabolism by CYP1A2, CYP2D6 and CYP3A out of which CYP1A2 is expected to contribute ~53%. Therefore, the highest expected increase in exposure of PF-06826647 based on CYP1A2 inhibition is ~2-fold. The predicted exposure margins for Total C_{max} and Total AUC with ~2-fold increase in exposure at the highest dose of 400 mg QD is approximately 0.94 and 1.67, respectively.

With maximum expected increase in exposure of PF-06826647 due to interaction with EE, the maximum expected erythropoietin (EPO) inhibition at 400 mg QD will be approximately 80%. Reticulocyte count and hemoglobin level will be monitored on a regular basis in the study for safety CCI for EPO inhibition.

The Phase 1 study (C2501001) demonstrated an acceptable safety profile at single doses of PF-06826647 ranging from 3 mg to 1600 mg in the single ascending portion and ten-day doses from 10 mg to 1200 mg daily in the multiple ascending portion of the study. Dose escalation stopping rules were not triggered. There were no clinically meaningful findings in vital signs, ECGs, or potential Hy's Law cases reported during this study. In addition, there were no serious AEs (including death) or suspected, unexpected, serious adverse reactions (SUSARs) reported. All reported Treatment Emergent Adverse Events (TEAEs) were of mild intensity.

The 200 mg and 400 mg doses were selected for the Extension Treatment Period due to the higher projected PASI 90 response rates at these doses. Based on the exposure-response modeling with the PASI data observed up to Week 4, the projected PASI 90 response rates at 200 mg and 400 mg are 47% and 83% at Week 16 respectively, while 50 mg and 100 mg are expected to provide <15% PASI 90 response rate.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities.

The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of Activities for the last participant in the trial globally.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 (or the minimum country-specific age of consent if >18) and 75 years, inclusive, at Screening.

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Participants with a diagnosis of plaque psoriasis (psoriasis vulgaris) for at least 6 months prior to Baseline/Day 1 (prior to first dose of study drug).

4. Have a PASI score of 12 or greater AND a Physician Global Assessment score of 3 ("moderate") or 4 ("severe") at Baseline/Day 1 (prior to first dose of study drug).

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Weight:

6. Body weight must be >40 kg.

Informed Consent:

7. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol.

8. Must discontinue systemic, topical and/or phototherapy therapies (eg, ultraviolet B (UVB) or photochemotherapy (PUVA)) for the treatment of psoriasis per timing criteria described in Section 5.2.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Currently have non-plaque forms of psoriasis, eg, erythrodermic, guttate, or pustular psoriasis, except for nail psoriasis which is allowed.

2. Evidence of other skin conditions (eg, eczema) at the time of screening or baseline visit that would interfere with the evaluation of psoriasis.

3. Current drug-induced psoriasis, eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, antimalarial drugs or lithium.

4. If receiving non-prohibited concomitant medications for any reason, must be on a stable regimen, which is defined as not starting a new drug or changing dosage within 7 days or 5 half-lives (whichever is longer) prior to first dose of study drug.

5. Any psychiatric condition including recent (within the past year) or active suicidal ideation or behavior that meets any of the following criteria:

    a. Suicidal ideation associated with actual intent and a method or plan in the past year: "Yes" answers on items 4 or 5 of the Columbia suicide severity rating scale (C-SSRS) (10.9).

    b. Previous history of suicidal behaviors in the past 5 years: "Yes" answer (for events that occurred in the past 5 years) to any of the suicidal behavior items of the C-SSRS.

    c. In the opinion of the investigator or Sponsor (or designee) exclusion is required.

6. Have any condition possibly affecting oral drug absorption, eg, gastrectomy, clinically significant diabetic gastroenteropathy, or certain types of bariatric surgery such as gastric bypass. Procedures such as gastric banding, that simply divide the stomach into separate chambers, are NOT exclusionary.

7. Have current or recent (within the past year) history of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiovascular, or neurological disease.

8. History of any lymphoproliferative disorder (such as Epstein-Barr virus [EBV] -related lymphoproliferative disorder, history of lymphoma, leukemia, or signs and symptoms suggestive of current lymphatic disease.

9. History (single episode) of disseminated herpes zoster or disseminated herpes simplex, or a recurrent (more than one episode of) localized, dermatomal herpes zoster.

10. History of infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator within 3 months prior to first dose of study drug or a history of infection requiring oral antimicrobial therapy within 2 weeks prior to first dose of study drug.

11. Infected with Mycobacterium tuberculosis (TB) (see Section 8.2.1.1).

12. Have known immunodeficiency disorder or a first-degree relative with a hereditary immunodeficiency.

13. History of recurrent (≥2) venous thrombosis or any arterial thromboembolism or known blood clotting disorders.

14. History of acute coronary syndrome (eg, myocardial infarction, unstable angina pectoris) and any history of cerebrovascular disease within 24 weeks before screening.

15. Have any malignancies or a history of malignancies except for adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.

16. Have undergone significant trauma or major surgery within 1 month prior to Screening or plan to undergo surgery during treatment period.

17. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study. For any reason in the opinion of the investigator or sponsor, the participant is inappropriate for entry into this study.

Prior/Concomitant Therapy:

18. Planned initiation of, or changes to, concomitant medication that could affect psoriasis (eg, beta blockers, calcium channel blockers, antimalarial drugs or lithium) are to occur within 2 weeks prior to randomization and/or during the study.

19. Are taking or require oral or injectable (eg, intraarticular, intramuscular or intravenous) corticosteroids for any condition. (Must be discontinued for at least 4 weeks prior to first dose of study drug).

20. Have been vaccinated with live or attenuated live vaccine within the 6 weeks prior to the first dose of study drug or expects to be vaccinated with these vaccines during treatment, or within the 8 weeks following the last dose of study drug. (For further information regarding avoidance of household contacts who may be vaccinated see Section 5.3.2).

21. Require treatment with prohibited concomitant medications(s) (see Section 6.5) or have received a prohibited concomitant medication/dietary supplement within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study drug. Details include specific discontinuation recommendations and, additional details are found in Appendix 8.

22. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of investigational product used in this study (whichever is longer).

Diagnostic Assessments:

23. Known history of incompletely treated hepatitis B or C, or human immunodeficiency virus (HIV) based on documented history with positive serological test, or positive HIV serological test at screening.

    - Participants who are hepatitis C antibody (HCVAb) positive require further testing with Hepatitis C virus (HCV) ribonucleic acid (RNA) Polymerase chain reaction (PCR) may be eligible if HCV RNA PCR is negative.

    - Participants who are hepatitis B surface antigen (HBsAg) negative and hepatitis B core antibody (HBcAb) positive will be reflex tested for Hepatitis B Surface Antibody (HBsAb). If HBsAb is positive, participant may be eligible. If HBsAb is negative, the participant is not eligible. This reflex test applies to all countries except Japan.

    - Participants who are negative for all three serology tests may be eligible.

    - Participants who are HBsAg positive are not eligible.

    - In **Japan ONLY**, *all* participants will undergo testing for all three tests HBsAg, HBcAb, and HBsAb during Screening.

        - Participants who have negative HBsAg, positive HBcAb, and negative HBsAb are not eligible.

        - Participants who have negative HBsAg, negative HBcAb and positive HBsAb and provide a documentation of prior Hepatitis B Virus (HBV) vaccination may be eligible and will not require HBV DNA monitoring during the study.

        - Participants who have negative HBsAg, negative HBcAb and positive HBsAb *without* documentation of prior HBV vaccination, and who have negative HBsAg, positive HBcAb and positive HBsAb are required to undergo HBV DNA reflex testing.

            - Participants with detectable HBV DNA are not eligible.

- Participants without detectable HBV DNA may be eligible. If enrolled, HBV DNA will be assessed at Weeks 12 (Investigational Treatment Period), Weeks 24, 36 (Extension Treatment Period) and ET (if applicable).

24. Screening or baseline standard 12-lead electrocardiogram (ECG) that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline corrected QT [QTc] interval >450 millisecond (msec), complete left bundle branch block [LBBB], signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree atrioventricular [AV] block, or serious bradyarrhythmias or tachyarrhythmias). If the baseline uncorrected QT interval is >450 msec, this interval should be rate-corrected using the Fridericia method and the resulting corrected QT interval by Fridericia (QTcF) should be used for decision making and reporting. If QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTc or QRS values should be used to determine the participant's eligibility. Computer-interpreted ECGs should be over read by a physician experienced in reading ECGs before excluding participants.

25. Participants with ANY of the following abnormalities in clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat, if deemed necessary:

    - Hemoglobin <11.0 g/dL or hematocrit <30% (<0.30 v/v);
    - White blood cell count <3.0 x 10^9/L (<3000 mm^3);
    - Absolute lymphocyte count of <1.0 x 10^9/L (<1000/mm^3);
    - Absolute neutrophil count of <1.5 x 10^9/L (<1500/mm^3);
    - Platelet count <100 x 10^9/L (<100,000/mm^3);
    - eGFR (estimated glomerular filtration rate) <60 mL/min/1.73 m^2 using serum creatinine based on the Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) calculation;
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values >2 times the upper limit of normal (ULN);
    - Total bilirubin ≥1.5 times the ULN; participants with a history of Gilbert's syndrome may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin is <ULN.

In the opinion of the investigator or sponsor, any uncontrolled clinically significant laboratory abnormality that would affect interpretation of study data or the participant's participation in the study.

Other Exclusions:

26. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or Sponsor employees, including their family members, directly involved in the conduct of the study.

27. Have a history of alcohol or substance abuse, unless in full remission for greater than 6 months prior to Day 1.

5.3. Lifestyle Considerations

In order to participate in the study, participants must be made aware of the following life style guidelines and restrictions that apply during and after the study period. Details of these life style guidelines are provided in sections as noted.

- On appropriate study visit days, comply with fasting requirement (water only) for at least 8 hours prior to the visit, as indicated in the Schedule of Activities.

- On study visit days, do not smoke or ingest caffeine (eg, tea, coffee, some soft drinks/colas/energy drinks and power bars) during the 30 minutes prior to blood pressure and pulse rate measurements.

- Only on study visit days, do not take the dose of study drug until instructed to do so by the investigator or designated study site staff while at the study site.

- On study visit days, showering or bathing is permitted prior to attending the study visit, but do not moisturize.

- On study visit days, take prescribed permitted concomitant medication, as needed, prior to the study visit, if it can be administered with water only. Prescribed permitted concomitant medications that must be taken with food or after meals should not be taken until after the visit procedures have been completed.

- Contact the study site investigator if there are any changes or additions to concomitant medications.

- As needed, participants may use the treatments listed as permitted in Section 6.5 for the specified body sites described. On clinic visit days, do not use any of these treatments until after the clinic visit is completed.

- Abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, and aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace is permitted.

- Avoid prolonged exposure to the sun and avoid use of tanning booths or other ultraviolet light sources during the study.

- Herbal supplements must be discontinued 28 days prior to the first dose of study medication. Refrain from excessive consumption of grapefruit or grapefruit juice or citrus fruits eg, Seville oranges, pomelos within 7 days prior to the first dose of study medication It is recommended that participants avoid excessive consumption of grapefruit or grapefruit juice or citrus fruits eg, Seville oranges or pomelos not to exceed 8 ounces (~240 mL) total in a day while in the study.

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4 Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities (SoA), the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 or 2 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

Female participants using hormonal contraceptives are required to use an additional acceptable barrier method listed in Contraception (Section 10.4.4) during the study and until 28 days after the last dose of study drug.

5.3.2. Vaccination

Vaccination with live virus, attenuated live virus, or any live viral components is prohibited within the 6 weeks prior to Day 1, during the study, and within the 8 weeks following the last dose of study drug. Similarly, current routine household contact with individuals who have been vaccinated with live vaccine components should be avoided in the same period. This is due to the potential for virus to be shed in bodily fluids (including stool) following vaccination with live component vaccines, leading to a potential risk that the virus may be transmitted.

Such vaccines include: FluMist® (intranasal influenza vaccine), attenuated rotavirus vaccine, varicella (chickenpox) vaccine, attenuated typhoid fever vaccine, oral polio vaccine, measles, mumps, rubella (MMR) vaccine and vaccinia (smallpox) vaccine.

5.3.3. Other Lifestyle Requirements

In order to participate in the study, participants must be made aware of the following life style guidelines and restrictions that apply during and after the study period. Details of these life style guidelines are provided in sections as noted.

1. On appropriate study visit days, comply with fasting requirement (water only) for at least 8 hours prior to the visit, as indicated in the Schedule of Activities.

2. On study visit days, do not smoke or ingest caffeine (eg, tea, coffee, some soft drinks/colas/energy drinks and power bars) during the 30 minutes prior to blood pressure and pulse (heart) rate measurements.

3. Only on study visit days, do not take the dose of study drug until instructed to do so by the investigator or designated study site staff while at the study site.

4. On study visit days, showering or bathing is permitted prior to attending the study visit, but do not moisturize.

5. On study visit days, take prescribed permitted concomitant medication, as needed, prior to the study visit, if it can be administered with water only. Prescribed permitted concomitant medications that must be taken with food or after meals should not be taken until after the visit procedures have been completed.

6. Contact the study site investigator if there are any changes or additions to concomitant medications.

7. As needed, participants may use the treatments listed as permitted in Section 6.5 for the specified body sites described. On clinic visit days, do not use any of these treatments until after the clinic visit is completed.

8. Abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, and aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace is permitted.

9. Avoid prolonged exposure to the sun and avoid use of tanning booths or other ultraviolet light sources during the study.

10. Herbal supplements must be discontinued 28 days prior to the first dose of study medication.

    Refrain from excessive consumption of grapefruit or grapefruit juice or citrus fruits eg, Seville oranges, pomelos or within 7 days prior to the first dose of study medication. It is recommended that participants avoid excessive consumption of grapefruit or grapefruit juice or citrus fruits eg, Seville oranges or pomelos exceeding 8 ounces (~240 mL) total in a day while in the study.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to investigational product. Screen failure data are collected and remain as source and are not reported to the clinical database. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE). Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once.

Re-screened participants will be re-consented. All screening assessments must be repeated during re-screening, with the exception of chest radiograph, HIV, Hepatitis and TB testing, provided re-screening is done within 3 months of screening.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, the term investigational product may be used synonymously with study intervention.

6.1. Study Intervention(s) Administered

Blinded PF-06826647 and matching placebo will be provided as tablets for oral administration. PF-06826647 will be provided in dosage strengths of 100 mg and 25 mg tablets. PF-06826647 and matching placebo will be supplied in blister cards and labeled according to local regulatory requirements.

Intervention Name	PF-06826647	PF-06826647	PF-06826647	PF-06826647	Placebo
ARM Name	PF-06826647 50 mg	PF-06826647 100 mg	PF-06826647 200 mg	PF-06826647 400 mg	Placebo
Type	Drug	Drug	Drug	Drug	Drug
Dose Formulation	Tablet	Tablet	Tablet	Tablet	Tablet
Dosage Level(s)	50 mg QD	100 mg QD	200 mg QD	400 mg QD	Placebo
Number and Type of Tablets During Investigational Treatment Period, Day 0 to Week 16 (Number of Tablets)	2 x 25 mg active, and 4 x 100 mg size placebo	2 x 25 mg size placebo, and 1 x 100 mg active, and 3 x 100 mg size placebo	2 x 25 mg size placebo, and 2 x 100 mg active, and 2 x 100 mg size placebo	2 x 25 mg size placebo, and 4 x 100 mg active	2 x 25 mg size placebo, and 4 x 100 mg size placebo
Number and Type of Tablets During Extension Treatment Period, Week 16 to Week 40 (Number of Tablets)	2 x 100 mg active, and 2 x 100 mg size placebo or 4 x 100 mg active	2 x 100 mg active, and 2 x 100 mg size placebo or 4 x 100 mg active	2 x 100 mg active, and 2 x 100 mg size placebo	4 x 100 mg active	2 x 100 mg active, and 2 x 100 mg size placebo or 4 x 100 mg active
Route of Administration	Oral	Oral	Oral	Oral	Oral
Investigational Medicinal Product (IMP) and Noninvestigational Medicinal Product (NIMP)	IMP	IMP	IMP	IMP	N/A
Sourcing	Provided centrally by the sponsor IP should be provided as outlined in the Investigational Product Manual.	Provided centrally by the sponsor IP should be provided as outlined in the Investigational Product Manual.	Provided centrally by the sponsor IP should be provided as outlined in the Investigational Product Manual.	Provided centrally by the sponsor IP should be provided as outlined in the Investigational Product Manual.	Provided centrally by the sponsor IP should be provided as outlined in the Investigational Product Manual.
Packaging and Labeling	Study intervention will be provided as tablets in blinded blister cards. Each blister card will be labeled as required per country requirement.	Study intervention will be provided as tablets in blinded blister cards. Each blister card will be labeled as required per country requirement.	Study intervention will be provided as tablets in blinded blister cards. Each blister card will be labeled as required per country requirement.	Study intervention will be provided as tablets in blinded blister cards. Each blister card will be labeled as required per country requirement.	Study intervention will be provided as tablets in blinded blister cards. Each blister card will be labeled as required per country requirement.

Participants will receive blinded labeled supplies throughout the study. To accomplish this, all participants will take a total of six tablets per day during the Investigational Treatment Period, and four tablets per day during the Extension Treatment Period.

The participants continuing into the Extension Treatment Period that were originally randomized to the 200 mg and 400 mg treatment groups in the Investigational Treatment Period will continue on their respective doses, while those randomized to one of the other treatment groups including placebo will be randomly assigned at study baseline to either receive 200 mg or 400 mg during the Extension Treatment Period.

6.1.1. Administration

Participants will swallow the investigational product (IP) whole and will not manipulate or chew the IP prior to swallowing. Participants will administer IP as outpatients, except on study visit days. On study visit days, participants should not take their dose of study drug until instructed to do so by the investigator or designated study site staff while at the study site.

Blinded PF-06826647 tablets and matching placebo for oral administration will be dispensed in blisters. Participants will be provided dosing instructions.

Sites will be trained on how participants should take tablets at home through an Investigational Product manual and/or other vehicle(s). Sites are responsible for communicating this information to participants; and site staff should review the dosing instructions with participants at every study visit.

Participants should take the IP orally once daily during the Investigational Treatment Period and the Extension Treatment Period of the study.

A temporary hold on dosing of the investigational product during the study for an individual participant for up to a maximum of 7 consecutive days is allowed once from Day 1 to Day 113, if the principal investigator (PI) deems it necessary because of infections (eg, upper respiratory infection, urinary tract infection), gastrointestinal (GI) disorders (eg, diarrhea, nausea, vomiting) or hematological abnormalities. Any temporary hold on dosing of the investigational product during the study should be recorded in the case report form (CRF).

It is recommended that the tablets be swallowed whole with ambient temperature water to a total volume of approximately 240 mL, and not to manipulate or chew the medication prior to swallowing; and **it is recommended to be taken with food**. On study visit days, participants are to be instructed to refrain from dosing at home and are to take the dose in the clinic from their current blister card and the dose from the newly dispensed blister card will be taken on the next day at home.

If a dose is missed and the interval to the next dose is less than 8 hours, the missed dose should not be administered.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention, as applicable for temperature-monitored shipments.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperature since previously documented for all site storage locations upon return to business.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All study interventions will be accounted for using an investigational product accountability form/record. The participant will be asked to bring all dispensed investigational product (including empty, partially used and unused blister packs) and the dosing diary to the clinic at every visit. Detailed drug accountability records will be maintained by study staff for each participant.

4. Further guidance and information for the final disposition of unused study interventions are provided in the investigational product (IP) manual.

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

6. Study interventions should be stored in their original containers and in accordance with the labels.

7. Site staff will instruct participants on the proper storage requirements for take-home study intervention.

8. Any excursions from the study intervention label storage conditions should be reported to the sponsor upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until the sponsor provides permission to use the study intervention. It will not be considered a protocol deviation if the sponsor approves the use of the study intervention after the temperature excursion. Use of the study intervention prior to the sponsor's approval will be considered a protocol deviation. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

9. The sponsor or designee will provide guidance on the destruction of unused study intervention (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by the sponsor, and all destruction must be adequately documented.

Additional details about accountability, storage, destruction, and excursion reporting can be found in the IP manual.

6.2.1. Preparation and Dispensing

The investigational product will be dispensed using an interactive response technology (IRT) drug management system at each visit per SoA. A qualified staff member will dispense the investigational product via unique container numbers in the blister cards provided, in quantities appropriate for the study visit schedule. The participant/caregiver should be instructed to maintain the product in the blister cards provided throughout the course of dosing and return the blister cards (including empty, partially used and unused blister packs) to the site at the next study visit.

6.2.2. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record. All blister cards of investigational product must be returned to the investigator by the participant at every visit and at the end of the trial.

The participant will be asked to bring all dispensed investigational product (including empty, partially used and unused blister packs) and the dosing diary to the clinic at every visit. Detailed drug accountability records will be maintained by study staff for each participant.

The original investigational product accountability log, or equivalent document, must be accurately completed, signed by the Investigator, and retained at the study site (with a copy supplied to the sponsor) when the study is complete.

6.2.3. Destruction of Investigational Product Supplies

The investigator will keep the entire investigational product returned by the participants until destruction is authorized.

The sponsor or designee will provide guidance on the destruction of unused study intervention (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by the sponsor, and all destruction must be adequately documented.

Further guidance and information for the final disposition of unused study interventions are provided in the IP manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Allocation to treatment will occur via an Interactive Response Technology (IRT) system. The system will be programmed with blind-breaking instructions. Refer to subsections 6.3.1 Allocation to Investigational Product and 6.3.2 Breaking the Blind for further details.

6.3.1. Allocation to Investigational Product

Allocation of participants to treatment groups will proceed through the use of an interactive response technology (IRT) system (interactive Web-based response [IWR]). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the participant number. The site personnel will then be provided with a treatment assignment, randomization number, and dispensable unit (DU) or container number when investigational product is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

Investigational product will be dispensed at the study visits summarized in the SoA.

Returned investigational product must not be redispensed to the participants.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.3.2. Breaking the Blind

At the initiation of the study, the investigator site will be instructed on the method for breaking the blind. The method will be an electronic process. The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. However, discussion with the sponsor in advance of unblinding is not required. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF). Any cases of unblinding will be documented in the clinical study report. The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

The participant will take the investigational product at home; compliance will be captured daily by the participant using a Dosing Diary and instructions provided by the site. The participant will be instructed to complete the Dosing Diary (each time investigational product is provided in the clinic or at home) starting with the first dose provided in the clinic on Day 1, then daily through Week 16 and through Week 40.

Participant compliance with investigational product will be assessed at each visit. If a visit is missed consult the Medical Monitor. Compliance will be assessed by review of the participant-completed Dosing Diary and source documents will be placed in the participant's study file. Participants will be instructed to bring the Dosing Diary and all dispensed investigational product supplies in the original packaging (used as well as unused) to every study visit.

Non-compliance is defined as less than 80% or more than 120% of IP dosing as directed by the dosing instructions. The investigator and the sponsor have the discretion to withdraw any participant from the study for reasons of non-compliance with the dosing regimen. Investigators should indicate on the appropriate CRF page noncompliance with study intervention and provide an explanation. Inventory control of all investigational products must be rigorously maintained throughout the duration of the study until all medication has been accounted for and/or returned to the sponsor. Any discrepancies noted between drug dispensing records and the drug inventory must be reported to the sponsor.

6.5. Concomitant Therapy

Permitted Concomitant Medication

Body Region	Permitted Topical Treatments
Palms, soles, face, and intertriginous areas	Low or least potent (Class 6 or 7) topical corticosteroids Hydrocortisone ≤1% and hydrocortisone acetate ≤1% are the only topical corticosteroids permitted
Scalp	Tar preparations Salicylic acid preparations Shampoos free of corticosteroids
All body regions	Study supplied non-medicated emollient, Cetaphil® moisturizing cream

Prohibited Concomitant Medications

1. The following hydrocortisones are NOT permitted:
    - Hydrocortisone 17 butyrate.
    - Hydrocortisone valerate.
    - Hydrocortisone/hydrocortisone acetate with concentration higher than 1%.

2. If received any of the following treatment regimens, for any reason, are eligible providing the following minimum washout criteria are observed:

   Must be discontinued for at least **12 weeks** prior to first dose of study drug:

   a. Any investigational or experimental therapy or procedure for psoriasis, psoriatic arthritis or rheumatoid arthritis;

   b. efalizumab (Raptiva®), secukinumab (Cosentyx) or Ixekizumab (Taltz) or other anti-IL-17, tofacitinib (Xeljanz) or treatment with apremilast (Otezla).

   Must be discontinued for at least **10 weeks** prior to first dose of study drug:

   a. Adalimumab (Humira®);

   b. Certolizumab pegol (Cimzia®);

   c. Infliximab (Remicade®);

   d. Alefacept (Amevive®).

   Must be discontinued for at least **4 weeks** prior to first dose of study drug:

   a. Etanercept (Enbrel®);

   b. Systemic treatments other than biologics that could affect psoriasis, eg, oral or injectable (eg, intraarticular, intramuscular, or intravenous) corticosteroids, retinoids, methotrexate, cyclosporine, fumaric acid derivatives, sulfasalazine, hydroxycarbamide (hydroxyurea), azathioprine, intramuscular gold;

   c. Psoralen + UVA phototherapy (PUVA).

   Must be discontinued for at least **2 weeks** prior to first dose of study drug:

   a. Topical treatments that could affect psoriasis, eg, corticosteroids, tars, keratolytics, anthralin, vitamin D analogs, and retinoids.

   b. Exceptions – the following **topical treatments** are allowed: non medicated emollients for use over the whole body; low or least potent (Class 6 or 7) topical corticosteroids for the palms, soles, face, and intertriginous areas only; tar and salicylic acid preparations for the scalp only, and shampoos free of corticosteroids for the scalp only. See details in Permitted Concomitant Topical Psoriasis Treatments.

   c. UVB (narrowband or broadband) phototherapy.

3. Any cell-depleting agents including but not limited to rituximab within 12 months of first dose of study drug or 5 half-lives (if known), whichever is longer, or until lymphocyte count returns to normal, whichever is longer.

4. Any prior treatment with ustekinumab (Stelara®), guselkumab (gene recombinant), risankizumab (gene recombinant) or non B cell-specific lymphocyte depleting agents/therapies (eg, alemtuzumab [CamPath®], alkylating agents [eg, cyclophosphamide or chlorambucil], total lymphoid irradiation, etc); participants who have received rituximab or other selective B-lymphocyte depleting agents (including experimental agents) within **6 months** of first dose of study drug or 5 half-lives (if known), whichever is longer, or until lymphocyte count returns to normal, whichever is longer.

5. Participants who are likely to receive during the study any moderate-strong CYP1A2 and CYP3A4 inhibitors/inducers or CYP2D6 inhibitors or MATE substrates as listed in Appendix 8.

Participants will abstain from all concomitant medications as described in Exclusion sections of the protocol and Appendix 8 Prohibited Concomitant Medications.

Participants should be instructed at each visit to contact the study site investigator promptly if there are any intended changes or additions to concomitant medications.

It is recommended that participants avoid changing other prescription or non-prescription drugs, vitamins, and dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study medication and throughout the study.

All concomitant medication taken during the study must be recorded with indication, daily dose, and start and stop dates of administration.

Medications taken after informed consent is obtained (but before the first dose of study medication) will be documented as prior medications. Medications taken after the first dose of study drug has been administered will be documented as concomitant medications.

6.5.1. Rescue Medicine

There is no rescue therapy to reverse the adverse events (AEs) observed with PF-06826647; standard medical supportive care must be provided to manage the AEs.

6.6. Dose Modification

Treatment assignment in the Extension Treatment Period will be predetermined according to the Scheme shown in Section 1.2. Participants who are in the placebo, 50 mg, or 100 mg treatment arms will be assigned to either 200 mg or 400 mg PF-06826647 in the Extension Treatment Period. Allocation to either dose in the Extension Treatment Period will be based on an initial treatment assignment at randomization. No dose adjustment is allowed during the study.

6.7. Intervention after the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue the investigational product. Per the study estimands, if investigational product is permanently discontinued, the participant will proceed to Early Termination per Schedule of Activities. The site will inform sponsor medical monitor or sponsor clinician if the below criteria for permanent discontinuation of the IP are triggered.

Any participant meeting discontinuation criteria must have an Early Termination visit with their first visit occurring 1 week after their last dose whenever possible and continue visits per Investigator's discretion until the event has returned to normal or baseline levels or is deemed clinically stable.

The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information.

Note that discontinuation of the investigational product does not represent withdrawal from the study.

Participants experiencing a thrombotic event as part of a serious adverse event must be discontinued from further IP administration and referred to a specialist for further evaluation of possible hypercoagulable state, as per local guidelines.

ECG Changes

A participant who meets either bulleted criterion below based on the average of triplicate ECG readings will be withdrawn from the IP administration.

- QTcF >500 msec;
- Change from baseline: QTc >60 msec.

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QTcF after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

Laboratory Abnormalities

All the following laboratory abnormalities require discontinuation if they are confirmed. Confirmation through re-testing should occur within 48 hours:

Laboratory Variable	Laboratory Value
Hematology	
Absolute Neutrophil Count	<1000/mm^3; <1.0 x10^9/L
Hemoglobin	<10.0 g/dL; <6.2 mmol/L; <100 g/L
Platelet count	<75,000/mm^3; <75.0x10^9/L
Lymphocytes	<500/mm^3; <0.5x10^9/L
Chemistry	
AST[a]	>3x ULN
ALT[a]	>3x ULN
Total bilirubin[b]	>1.5x ULN

a. Additional investigations, such as review of ethanol, recreational drug and dietary supplement consumption should be done; testing for acute hepatitis A, B or C infection and biliary tract imaging should be promptly discussed with sponsor medical monitor.

b. Total bilirubin >1.5 x ULN; participants with a history of Gilbert's syndrome may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin is <ULN.

Pregnancy

If pregnancy is confirmed by serum beta human chorionic gonadotropin (β-hCG) testing at any time, then the sponsor clinician or sponsor medical monitor should be notified immediately.

Suicidality

Participants triggering criteria for suicidal ideation and behavior as described in Section 8.2.5.1.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

At the time of discontinuing from the study, if possible, an early termination visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The Early Termination visit applies only to participants who are randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal. The participant will be permanently discontinued both from the study intervention and from the study at that time.

If a participant withdraws from the study, he/she may request destruction of any remaining samples, but data already generated from the samples will continue to be available and may be used to protect the integrity of existing analyses. The investigator must document any such requests in the site study records.

If the participant withdraws from the study and also withdraws consent (see below) for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the Clinical Trial (CT) SAE Report.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

For participants who discontinue early from the Investigational Treatment Period prior to the Week 16 visit, or those who discontinue early from the Extension Treatment Period prior to the Week 40 visit, should perform the procedures scheduled at the Early Termination (ET) visit.

See Section 10 for Guidelines for Safety Monitoring and Discontinuations.

Withdrawal of Consent:

Participants who request to discontinue receipt of study treatment will remain in the study and proceed to ET visit as soon as possible. Whenever possible, these participants should have one visit approximately two weeks after the last dose (Week 20 or 44 Follow up visit assessments) and/or at least 28 days after the last dose of IP was administered.

The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant as noted below.

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- The investigator should inquire about the reason for withdrawal, request that the participant return all unused investigational product(s), request that the participant return for a final visit, if applicable, and follow up with the participant regarding any unresolved adverse events (AEs);

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants will be outlined in the Lab Manual. Additional blood samples may be taken for safety assessments at times specified by Sponsor, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy Assessments

Measures of psoriasis efficacy that will be collected throughout the study are outlined in this section. These efficacy measures will be evaluated by an experienced physician, dermatologist, or qualified medical professional and should be performed by the same clinician throughout the study whenever possible.

Detailed descriptions for the PGA and patient reported outcomes (PROs) are provided in Appendices 10-17.

8.1.1. Psoriasis Area and Severity Index (PASI)

The Psoriasis Area and Severity Index quantifies the severity of a participant's psoriasis based on both lesion severity and the percentage of body surface area affected.

Lesion severity: the basic characteristics of psoriatic lesions – erythema, induration and scaling – provide a means for assessing the severity of lesions. Assessment of these three main signs is performed separately for four areas of the body: head, upper limbs, trunk, and lower limbs. Average erythema, induration and scaling are rated for each body area according to a 5-point scale: 0, no involvement; 1, slight; 2, moderate; 3, marked; 4, very marked.

Body surface area (BSA) involvement: the extent (%) to which each of the four areas of the body is affected by psoriasis is assigned a numerical score according to the following area scoring criteria: 0, no involvement; 1, >0 to 9%; 2, 10 to 29%; 3, 30 to 49%; 4, 50 to 69%; 5, 70 to 89%; 6, 90 to 100%.

Component Scoring Criteria for the Psoriasis Area and Severity Index (PASI)

Component Score		**Description**
Erythema (E)		
0	No involvement	None; may have residual hyperpigmentation
1	Slight	Pink or light red
2	Moderate	Darker pink-red
3	Marked	Red
4	Very Marked	Extremely red, “beefy” red
Induration (I)		
0	No involvement	None
1	Slight	Minimal elevation relative to normal surrounding skin
2	Moderate	Easily palpable with rounded edges
3	Marked	Elevated with hard, sharp borders
4	Very Marked	Very elevated with very hard, sharp borders
Scaling (S)		
0	No involvement	None
1	Slight	Mainly fine scale, some lesion partially covered
2	Moderate	Coarser thin scale, most lesions partially covered
3	Marked	Coarser thick scale, nearly all lesions covered, rough
4	Very Marked	Very thick scale, all lesions covered, very rough

Percent BSA with Psoriasis: the extent (%) to which each of the four body regions is involved with psoriasis is categorized using a non-linear scaling method to a numerical area score according to the following BSA scoring criteria (Table 4).

Table 4. Psoriasis Area and Severity Index (PASI) Area Score Criteria

Percent Body Surface Area (BSA) with Psoriasis	**Area Score**
0% (no involvement)	0
>0-9%	1
10-29%	2
30-49%	3
50-69%	4
70-89%	5
90-100%	6

Calculating PASI

Body Region Weighting: each body region is weighted according to its approximate percentage of the whole body (Table 5).

Table 5. Psoriasis Area and Severity Index (PASI) Area Score Criteria

Body Region	Body Region Weighting
Head and Neck	0.1
Upper Limbs	0.2
Trunk (including axillae and groin)	0.3
Lower Limbs (including buttocks)	0.4

In each body region, the sum of the Severity Scores for erythema, induration and scaling is multiplied by the Area Score and by the Body Region Weighting to provide a body region value, which is then summed across all four body regions resulting in a PASI score as described in the following equation:

$$PASI = 0.1Ah(Eh + Ih + Sh) + 0.2Au(Eu + Iu + Su) + 0.3At(Et + It + St) + 0.4Al(El + Il + Sl)$$

where A = Area Score; E = erythema; I =induration; S = scaling; h = head; u = upper limbs; t = trunk; l = lower limbs.

The PASI score can vary in increments of 0.1 units from 0.0 to 72.0, with higher scores representing increasing severity of psoriasis. The PASI score will be used for the primary analysis.

Calculation of PASI will be done centrally by sponsor programmers.

Linear Method Psoriasis Area and Severity Index (L PASI)

A second method of calculating PASI will also be performed. A linear scaling method will be applied to the Psoriasis Area and Severity Index calculation, adapting the classic calculation by using the actual percentage body surface area involved in psoriasis rather than categorizing the percentage involvement on a 7 point scale.

The linear scaling method will be calculated from the study database; investigator sites will only perform the classic PASI calculation during the study. The L PASI score will be used for a sensitivity analysis.

L-PASI Calculation

$$L\text{-}PASI = 0.1(6xBh)x(Eh + Ih + Sh) + 0.2(6Bu)x(Eu + Iu + Su) + 0.3(6xBt)x(Et + It + St) + 0.4(6xBl)x(El + Il + Sl)$$

where B = percentage area of involvement; E = erythema; I =induration; S = scaling; h = head; u = upper limbs; t = trunk; l = lower limbs

8.1.2. Physician Global Assessment (PGA)

The Physician Global Assessment of psoriasis is scored on a 5-point scale, reflecting a global consideration of the erythema, induration and scaling across all psoriatic lesions. Average erythema, induration and scaling are rated separately over the whole body according to a 5-point severity scale, scored from 0 to 4, with appropriate morphologic descriptors. The severity rating scores are summed and the average taken – the total average is rounded to the nearest whole number score to determine the PGA (See Appendix 17).

The 5-point scale for PGA is: 0, "clear"; 1, "almost clear"; 2, "mild"; 3, "moderate"; 4 "severe" (Table 7).

Table 6. Component Scoring Criteria for the Physician's Global Assessment (PGA)

Score	Description
Erythema (E)	
0	No evidence of erythema (post-inflammatory hyperpigmentation and/or hypopigmentation may be present)
1	Light pink
2	Light red
3	Red
4	Dark, deep red
Induration (I)	
0	No evidence of plaque elevation
1	Barely palpable
2	Slight, but definite elevation, indistinct edges
3	Elevated with distinct edges
4	Marked plaque elevation, hard/sharp borders
Scaling (S)	
0	No evidence of scaling
1	Occasional fine scale
2	Fine scale predominates
3	Coarse scale predominates
4	Thick, coarse scale predominates

Table 7. Physician's Global Assessment (PGA) Score

Physician's Global Assessment		Description
0	Clear	Cleared, except for any residual discoloration
1	Almost Clear	Majority of lesions have individual scores for (E + I + S)/3 that rounds to 1
2	Mild	Majority of lesions have individual scores for (E + I + S)/3 that rounds to 2
3	Moderate	Majority of lesions have individual scores for (E + I + S)/3 that rounds to 3
4	Severe	Majority of lesions have individual scores for (E + I + S)/3 that rounds to 4

Note: Calculated arithmetic average of individual signs severity scores [(E + I + S)/3] is rounded to the nearest whole number score (eg, if total ≤2.49, score = 2; if total ≥2.50, score = 3). Calculation will be done centrally by sponsor programmers.

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8.1.4. Rater Qualifications

For specific rating assessments, only qualified raters will be allowed to evaluate and/or rate participants in this study. The minimum qualifications a rater must meet for each study rating assessment will be outlined in the Rater Assessment Manual provided to each participating site. The level of experience with the target population (or equivalent), specific scale experience (or equivalent), and certification required (if applicable) will be listed and used to determine whether a rater is approved for a given assessment. Proposed raters who do not meet specific criteria but who may be qualified based on unique circumstances may be individually reviewed by the study clinical team to determine whether or not a waiver may be issued. The rater must become certified to perform selected study assessments before they can participate in the conduct of the study. For specifically defined assessments, rater training and standardization exercises may be conducted, and written and signed documentation will be provided by the site for each rater's certification. In return, each site will be provided written and signed documentation outlining each rater's certification for specific study assessments. Recertification may be required at periodic intervals during the study. The raters who administer specific study assessments will be documented in a centralized location and all site staff who administer ratings will be verified in the site study documentation during the conduct of the study.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

8.2.1. Assessments at Screening only

8.2.1.1. Tuberculosis (TB) Testing

Participants should be screened for TB using an Interferon gamma release assay (IGRA) per local guidelines. IGRA will be tested during screening or within 12 weeks prior to Screening. The following are acceptable IGRA assays: T SPOT® TB test (preferable, where available), QuantiFERON® TB Gold In Tube test (QFT GIT) and QuantiFERON® TB Gold test (QFT G). Site personnel should follow the processing and analyses steps based on the assay chosen. Ensure incubation steps are followed as appropriate.

Documentation of IGRA product used and the test result must be in the participant's source documentation.

If the results of the IGRA are indeterminate, the test may be repeated once, and if a negative result is obtained, enrollment may proceed. A positive test on repeat is exclusionary.

Participants with repeat indeterminate IGRA results may be enrolled after consultation with pulmonary or infectious disease specialist that determines low risk of infection (ie, participant would be acceptable for immunosuppressant (eg, anti-TNF tumor necrosis factor) treatment without additional action).

Participants who test positive for QFT-G/QFT-GIT test, but in the opinion of the PI are at low risk of TB infection may be referred to pulmonary or infectious disease specialist for consultation and potential IGRA test repeated once. Participants will be eligible if the repeat test is negative before the randomization.

8.2.1.2. Chest Radiograph

Participants must have chest radiograph taken at Screening and read by a qualified radiologist. Documentation of the official reading must be located and available in the source documentation.

If chest radiograph has been taken within 12 weeks prior to Day 1 and read by a qualified radiologist as normal, this does not have to be repeated at screening, provided documentation is available.

Chest radiograph may include chest x-ray (posterior-anterior and lateral views are recommended, however local guidelines should be followed) or other appropriate diagnostic image (ie, computed tomography or magnetic resonance imaging [MRI]). Participants with evidence of currently active TB, general infections, heart failure or malignancy will be excluded. Participants with changes suggestive of untreated latent or active TB infection may be enrolled after consultation with a pulmonary or infectious disease specialist who determines a low risk of infection.

8.2.1.3. Medical History

Investigators should make all reasonable efforts to obtain an accurate and complete medical history and history of prior medication use when evaluating whether a participant is eligible for the study. The following will be collected at Screening: complete medical history, psoriasis disease history (including disease duration and prior treatments), and alcohol and tobacco use history.

If the status of a participant's medical history is in doubt or information pertaining to a critical variable is conflicting, every reasonable step to secure proper documentation of correct medical status should be attempted. Documentation of the medical and medication histories over the protocol defined time periods should be available for sponsor review during the source data verification process. Questions about prior medications or eligibility should be directed to the sponsor clinician or sponsor medical monitor.

8.2.1.4. Suicidal Ideation and Behavior Risk Monitoring

The Columbia Suicide Severity Rating Scale (C-SSRS Appendix 9) is a validated tool to evaluate suicidal ideation and behavior.[11] At the screening and baseline visit, if there are "yes" answers on items 4, 5 in the past year, or on any question in the suicidal behavior section of the C-SSRS in the past 5 years, the participant will be excluded from the study.

8.2.2. Assessment During Study

8.2.2.1. Full Physical and Brief Physical Examinations

Full physical examinations must be performed by the investigator, sub-investigator, or a qualified healthcare professional per local guidelines. A full physical examination will include assessments of the general appearance, skin, head, eyes, ears, nose, throat, cardiovascular, respiratory (lung), gastrointestinal, and neurological systems. Investigators should pay special attention to clinical signs related to previous serious illnesses.

A brief examination will include assessments of the skin (both psoriasis and non-psoriasis skin) and body systems with any symptoms reported by the study participants.

Any clinically significant changes from the most recent physical examination should be recorded as adverse events (AEs). Investigators should pay special attention to clinical signs related to previous serious illnesses.

Full and brief physical exams will be performed as specified in Schedule of Activities.

8.2.2.2. Weight and Height

It is recommended that weight be measured in kilograms (kg) and that height be measured in centimeters (cm). Height and weight will be measured to one decimal place.

For measuring weight, a scale with appropriate range and resolution should be used and must be placed on a stable, flat surface. Participants should remove shoes, bulky layers of clothing, and jackets so that only light clothing remains.

8.2.2.3. Vital Signs (Blood pressure, pulse rate, and temperature)

Single sitting blood pressure (BP), pulse rate, and temperature will be measured at times specified in the Schedule of Activities. Additional collection times or changes to collection times will be permitted, as necessary to ensure appropriate collection of safety data.

Vital signs should be performed before laboratory blood collection after at least 5 minutes rest.

Sitting blood pressure (preferred but not required) will be measured with the participant's arm supported at the level of the heart and recorded to the nearest mm Hg. It is preferred that the same arm be used throughout the study.

The same size BP cuff, which has been properly sized and calibrated, will be used to measure BP each time. The use of automated devices for measuring BP and pulse rate is acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, it is preferred that vital signs be obtained prior to the nominal time of blood collection.

Body temperature may be collected using tympanic, oral (preferred), or axillary methods and that the same method be used consistently throughout the study.

8.2.3. Electrocardiograms

Six singlicate standard 12-Lead ECGs should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures pulse rate (PR), QT, and QTc intervals and QRS complex. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes. Consistent methods across visits is recommended.

ECGs should be performed before laboratory blood collection, BP, and pulse rate.

To ensure safety of the participants, a qualified individual (eg, sub-investigator) at the investigator site will make comparisons to baseline measurements taken at baseline. A copy of the ECG should be available as source documents for review. ECGs will be read locally during the dosing period.

If a postdose QTc interval remains ≥30 msec from the baseline **and** is >450 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator), or QTc intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than the criterion listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTc values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 7.

8.2.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.5. Suicidal Ideation and Behavior Risk Monitoring

Participants meeting exclusionary criteria (Section 5.2) for suicidal ideation/behavior will be excluded from study participation. It is recommended the participant's primary care physician (PCP) is informed if this exclusion criterion is met, and the participant referred to a mental health professional, either by the PCP or the investigator according to their usual practice.

8.2.5.1. Columbia Suicide Severity Rating Scale

The Columbia Suicide Severity Rating Scale (C-SSRS)[11] is a validated tool to evaluate suicidal ideation and behavior (Appendix 9). "Lifetime" version will be used at screening and baseline and the "since last visit" version will be used in all subsequent visits.

If at any visit, there are "YES" answers on items 4, 5 or on any behavioral question of the C-SSRS, a risk assessment should be done immediately by a qualified medical health practitioner for appropriate evaluation and treatment. If the participant cannot be seen by a mental health professional within 24 hours, then the participant should be sent to a local emergency room for psychiatric assessment. If these answers occurred after IP dosing (ie, post-Day 1), IP will be temporarily discontinued until further evaluation. This evaluation will help determine whether it is safe for the participant to continue to participate in the trial. Participants who answer "YES" on items 4, 5 or on any behavioral question of the C-SSRS on more than one occasion during a trial will be discontinued from the trial.

8.2.6. Herpetiform Rash Surveillance

For any occurrence of a suspected herpetiform rash (eg, herpes zoster and herpes simplex), specimens for viral deoxyribonucleic acid (DNA) analysis will be obtained: A swab of the affected area will be collected for confirmation; a blood sample for viral surveillance will be collected for the analysis of viral load. Details for these collections will be provided in the laboratory manual.

8.2.7. Glomerular Filtration Rate

Serum creatinine is the best known standard test for monitoring renal function. Serum creatinine will be measured as part of serum chemistry at times specified in the Schedule of Activities section of the protocol. Serum creatinine elevations above the ULN will be followed until resolution or baseline. Serum creatinine based eGFR will be calculated. eGFR will be calculated at corresponding times per Schedule of Activities.

The eGFR will be calculated using the equation developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).[12]

8.2.8. Pregnancy Testing

Pregnancy tests may be urine or serum tests, as indicated in SoA, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in women of child-bearing potential (WOCBP) at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced, and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving the investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE or that caused the participant to discontinue the PF-06826647 (see Section 7).

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days, except as indicated below, after the last administration of the investigational product.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF), not the AE section.

Follow-up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the CT SAE Report Form immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

SAEs occurring in a participant after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

During the active collection period, both nonserious AEs and SAEs are recorded on the CRF.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/ethics committees (ECs), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until at least 5 terminal half-lives or approximately 7 to 11 days after the last dose.

If a pregnancy is reported, the investigator should inform the sponsor within [24 hours] of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.5.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.3.6. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of PF-06826647 greater than 1600 mg of investigational product within a 24-hour time period will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities until PF-06826647 can no longer be detected systemically (at least 3 days).

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4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

5. Overdose is reportable to Safety **only when associated with an SAE**.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

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Unless prohibited by local regulations or IRB/EC decision, participants will be asked to indicate on the consent document whether they will allow their banked samples to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for patients. This component of the sampling banking is optional for participants; they may still participate in the study even if they do not agree to the additional research on their banked samples. The optional additional research does not require the collection of any further samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the laboratory manual.

8.9. Health Economics

Medical resource utilization is not evaluated in this study. However, the study does include the EQ5D-5L, a questionnaire that assesses patient preference for a given health state and which will be utilized for cost-effectiveness/utility modeling. The EQ5D-5L is summarized below in the patient reported outcomes measures section.

8.10. Patient Reported Outcome Measures

Every effort should be made for the participant to complete all patient reported outcome (PRO) questionnaires before any other assessments except at Baseline when eligibility needs to be confirmed. All PROs should be completed in the following order: Psoriasis Symptom Inventory (PSI), Peak-Pruritus Numerical Rating Scale (PP-NRS), CCI [redacted] will be completed as a diary from baseline to Day 15. Post Day 15, these scales will be completed at the site. At site visits participants will complete PROs in the following order: Psoriasis Symptom Inventory (PSI), PP-NRS, CCI [redacted] The amount of time required for a participant to complete the PRO questionnaires is approximately 10-25 minutes (depending on the visit and associated PROs).

Once participants meet all eligibility criteria, they will be provided a handheld device (provided by the sponsor) for the PSI (both 24-hour recall and 7-day recall), PP-NRS, a CCI [redacted] to be completed at home prior to first dose of the day. . All PROs are to be completed as per the time points defined in the Schedule of Activities.

Delegated site staff will oversee the use of electronic Patient Reported Outcomes (ePRO) devices. Completion of PROs will be monitored for adherence. Delegated site staff will review adherence to all applicable PROs with participants at each visit and counsel as appropriate. If a participant has repeated non-adherence, the participant should be retrained on use of the device. If a participant is unable to complete ePROs due to documented technical issue or disability or other limitation (eg, difficulty with manual dexterity or vision), the participant will be permitted to enter or remain in the study and a valid alternate

source of data entry is completed and reviewed by investigational site staff. This may include for example reading the questions verbatim to the participant and entering participant selection of responses by the site staff.

8.10.1. Psoriasis Symptom Inventory

The Psoriasis Symptom Inventory (PSI) is a self-administered 8 item questionnaire that measures the severity of psoriasis symptoms over the past 24 hours and the past 7 days (Appendix 10).[13] For the first 2 weeks up to Week 2 visit (inclusive), the PSI will be administered daily using a recall period of 24 hours. After Week 2 visit, the PSI will be administered according to the Schedule of Activities using a recall period of past 7 days. The measure includes concepts of itch, pain, burning, stinging, cracking, scaling, flaking, and redness. Participants are asked to respond to each item using a 5-point Likert response scale: 0: not all severe, 1: mild, 2: moderate, 3: severe and 4: very severe. PSI should be completed as described in the Schedule of Activities.

8.10.2. Peak-Pruritus Numerical Rating Scale

The intensity of pruritus will be assessed by a Peak-Pruritus Numerical Rating Scale (PP-NRS), an 11-category numeric rating scale from 0 to 10, which is patient reported (Appendix 11)[14,15] Participants will be asked to assess their itch over the past 24 hours, anchored by the terms “no itch” (0) and “worst itch imaginable” (10) at the ends.

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9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The primary estimand will be the population average treatment effect on PASI 90 rates at Week 16 relative to placebo without regard to compliance in the absence of prohibited medication. Measurements after the initiation of prohibited medication will be censored and treated as missing data. Missing data due to censoring, study withdrawal or other reasons will have data imputed using a control based multiple imputation strategy assuming these participants no longer receive an efficacy benefit from the IP but rather, have a response similar to participants assigned to placebo. The population based treatment effect will be the differences in the proportions of successes in each treatment arm compared to the corresponding placebo.

All other secondary continuous clinical endpoints will be analyzed using estimand E2, while all other key secondary categorical clinical endpoints will be analyzed using the primary estimand E1 as described above. CCI [redacted] Other estimands may be used for some of the primary and secondary endpoints as a means to examine the robustness of the results and to compare to

available literature as needed. Details of these analyses will be presented in the statistical analysis plan (SAP).

9.2. Sample Size Determination

The primary endpoint in this study is the PASI 90 response rate at Week 16. Assuming a PASI 90 response rate as 5% for the placebo group, and placebo corrected effect 35% or greater for one of the treatment groups, a total of N=128 completers are needed to ensure at least 90% power for the lower doses due to Bonferroni multiplicity adjustment with 1-sided type-I error rate of 5% and 2:1:1:2:2 allocation ratio of placebo, 50 mg, 100 mg, 200 mg, and 400 mg. The total sample size includes a sample size of 32 completers per arm for placebo, 200 mg and 400 mg, and 16 completers per arm for 50 mg and 100 mg. Accounting for a 20% chance of drop out, approximately a total of 160 participants will be enrolled in this study.

9.3. Populations for Analysis

For purposes of analysis, the following populations are defined:

Population	Description
Safety Analysis Set	All participants randomly assigned to IP and who take at least 1 dose of IP. Participants will be analyzed according to the product they actually received.

Defined Population for Analysis	Description
Modified Intention to Treat (mITT)	All participants randomly assigned to IP and who take at least 1 dose of IP.
CCI [redacted]	[redacted]

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary and key secondary: PASI 90 and PASI 75 at Week 16	A landmark analysis of the composite endpoint; achieving a PASI 90 response (a score of 90% improvement from Baseline) without prohibited medication, while remaining on study and providing data. The analysis will use the mITT analysis set. Based on the definition of the composite endpoint all participants in the mITT set will have a response for all visits (ie, there is no missing data). The proportions responding and the risk difference between treated arms and their corresponding placebo arm will be analyzed using an unconditional exact method: risk differences and corresponding 2-sided unconditional exact 90% confidence intervals will be computed using the Chan and Zhang (1999) method. Multiplicity adjustment will be utilized; details of multiplicity adjustment will be provided in the SAP.

Other continuous secondary endpoints at time points specified in the Schedule of Activities including; absolute PASI, change from baseline PASI, percent change from baseline PASI, absolute and change from baseline Itch Severity Score, absolute and change from baseline Psoriasis Symptom Inventory will be analyzed as described for the E2 estimand along with descriptive statistics and possibly graphical displays. No adjustments for multiplicity will be made for these endpoints.

Other binary secondary endpoints at time points specified in the Schedule of Activities including, PASI 50, PASI 100, PGA of clear or almost clear and proportions of participants achieving a Psoriasis Symptom Inventory Score of 0 or 1 will be analyzed as described for the primary estimand along with descriptive statistics and possibly graphical displays. No adjustments for multiplicity will be made for these endpoints.

CCI [redacted]

All endpoints in Extension Treatment Period will be analyzed with descriptive statistics and graphical displays when appropriate. Details of the analyses of the Investigational Treatment Period and Extension Treatment Period will be included in the Statistical Analysis Plan (SAP).

9.4.2. Safety Analyses

All safety analyses will be performed on the safety population.

Endpoint	Statistical Analysis Methods
Primary	The safety data will be summarized in accordance with Pfizer Data Standards. All participants who receive IP (safety population) will be included in the safety analyses. All safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations. Safety endpoints for the study include: • Treatment-emergent AEs and SAEs. • Withdrawals from active treatment due to AEs. • Serious infections, defined as any infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials. • Safety laboratory tests (eg, hematology [including coagulation panel], chemistry and lipid profiles). • Vital signs. Change from baseline on laboratory data and vital signs will be additionally summarized. Participant listings will also be produced for these safety endpoints.
CCI	[redacted]

9.4.2.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval, and QRS complex will be summarized by treatment and time.

The number (%) of participants with maximum postdose QTc values and maximum increases from baseline in the following categories will be tabulated by treatment:

Safety QTc Assessment

Degree of Prolongation	Mild (msec)	Moderate (msec)	Severe (msec)
Absolute value	>450-480	>480-500	>500
Increase from baseline		30-60	>60

In addition, participants with QTcF values >500 msec will be listed.

CCI

[redacted]

[redacted]

[redacted]

[redacted]

9.5. Interim Analyses

Interim analyses may be performed to assess efficacy and safety after at least 60% of the planned participants, ie, approximately 80 participants, complete their study participation through Week 12. Interim analysis results will be used for internal business decisions regarding future study planning or stopping for futility. Before the interim analysis is instigated, the details of the objectives, decision criteria, dissemination plan and method of maintaining the study blind as per Pfizer's SOPs will be documented and approved in the internal review committee (IRC) charter. In addition, the analysis details will be documented and approved in an interim analysis SAP or final SAP.

9.5.1. Data Monitoring Committee

This study will not use a data monitoring committee (DMC). This study will use an internal review committee (IRC) which will be comprised of internal Pfizer experts, independent of the study team.

Members of the study team will not be part of the IRC. An unblinded sponsor statistician or a clinician who is not directly involved with the study will perform the interim analyses and provide the results only to the IRC. No randomization information for individual participants will be reported to the IRC as part of the interim analysis; however, unblinded aggregate results will be reported.

The IRC will be responsible for evaluating safety of participants in the study according to the IRC Charter. The recommendations made by the IRC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

9.5.2. Safety Adjudication Committees

The identification of events requiring submission to an adjudication/review committee may be made by the study site and communicated to Pfizer or designee. Events requiring review, including cardiovascular and venous thromboembolic events may also be identified by the Pfizer study team or designee during the review of subject data listings or by site monitors during routine monitoring of participant's study records. The Pfizer study team or designee will notify the study site of any events if identified.

The Pfizer Study Team or designee will provide a listing of specific documents needed to support event adjudication by the Adjudication/Review Committees. Obtaining and submitting the documentation will be the responsibility of the study site. Event documentation will vary with the event requiring adjudication and may include (but not be limited to): hospital discharge summaries, operative reports, clinic notes, diagnostic tests, pathology reports, autopsy reports and death certificate information, as applicable.

CCI [redacted]

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;

- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines;

- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, investigator's brochure (IB), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;

- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;

- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Sponsor should be informed immediately.

In addition, the investigator will inform Sponsor immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is required to sign another ICD.

CCI [redacted]

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its standard operating procedures (SOPs).

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. US Basic Results are generally submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the European Medicines Agency (EMA) website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contribute to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included participant. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician participant chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the electronic CRF (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

10.1.8. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the contract research organization (CRO) if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, “publication”) before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study or Pfizer product related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, participant to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the clinical study agreement (CSA) between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study participants, and the CSA will control as to all other issues.

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the study team on demand (SToD) system.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Hematology[a]	Chemistry[a]	Urinalysis[a]	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Reticulocyte count Platelet count WBC count with differential Total neutrophils (%, Abs) Eosinophils (%, Abs) Monocytes (%, Abs) Basophils (%, Abs) Lymphocytes (%, Abs) Coagulation Panel Activated Partial Thromboplastin Time (aPTT) Prothrombin Time/International Normalized Ratio (PT/INR)	BUN/urea and creatinine Glucose Calcium Sodium Potassium Chloride Total CO2 (bicarbonate) AST, ALT GGT Total, indirect and direct bilirubin Alkaline phosphatase Uric acid Albumin Total protein Creatine kinase (CK) Lipid Profile Panel[b] Total Cholesterol Triglycerides HDL-C LDL-C	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[c]	At screening only: • FSH[d] • HIV • TB test[e] • HBsAg, HBcAb, HepB reflex (HBsAb), if applicable HCVAb and/or HBV[f]. At visits per SoA: • Pregnancy test (β-hCG)[g] • Skin swabs for herpetiform rash[h] • CCI [redacted]

Abbreviations: Abs = absolute; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; CO2 = carbon dioxide; FSH = follicle-stimulating hormone; GGT = Gamma Glutamyl Transferase; HBV= hepatitis B virus; HCV= hepatitis C virus; HDL = high density lipoprotein cholesterol; HIV = Human Immunodeficiency Virus; CCI [redacted] IGRA = Interferon Gamma Release Assay; INR = international normalized ratio; LDL =low density lipoprotein cholesterol; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; CCI [redacted] PCR = polymerase chain reaction; PPD = purified protein derivative; qual = qualitative; PT = prothrombin time; QFT-G = quantiferon-TB-Gold; RBC = red blood cell; CCI [redacted] WBC = white blood cell.

a. Safety labs include hematology, chemistry and urinalysis. Fasting not required unless lipid panel taken.

b. Lipid panel requires fasting (water only) at least 8 hours prior to collection.

c. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.

d. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women.

e. TB test must be Interferon Gamma Release Assay (IGRA).

f. HepB reflex testing only if HBsAg negative but HBcAb positive at Screening. If result of HCVAb is positive, or if Hepatitis C Virus antibody result is indeterminate, then an HCV RNA AMPLIPREP TAQMAN 2.0 will automatically be performed. HBV DNA monitoring may be applicable in Japan.

g. Serum/urine pregnancy test for WOCBP.

h. In cases of suspected herpetiform rash (eg, suspected herpes zoster and herpes simplex).

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the

participant's condition.

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect

Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE 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 participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None

Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	**None**	All (and exposure during pregnancy [EDP] supplemental form for EDP)

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the investigator's brochure (IB) and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as the data become available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Male Participant Reproductive Inclusion Criteria

No contraception methods are required for male participants in this study, as the calculated safety margin is ≥100-fold between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies.

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

  OR

- Is a WOCBP and using a contraceptive method that is acceptable and highly effective (with a failure rate of <1% per year), with high user dependency, as described below during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any study intervention(s). In addition, a second effective method of contraception, as described below, must be used (except for sexual abstinence).

  The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

  The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are *not* considered WOCBP:

1. Premenopausal female with 1 of the following:

   - Documented hysterectomy;
   - Documented bilateral salpingectomy;
   - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

   - A postmenopausal state is defined as age 60 years or older or no menses for 12 months without an alternative medical cause.

   - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).

   - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Highly Effective Methods with Low User Dependency are preferred. (Failure rate of <1% per year when used consistently and correctly).

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation*.

2. Intrauterine device (IUD).

3. Intrauterine hormone-releasing system (IUS)*.

4. Bilateral tubal occlusion.

5. Vasectomized partner:

   - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

** This requirement may be removed if supported by the outcome of ongoing oral contraceptive PK interaction study (Study C2501005); investigators will be notified and notifications as per local regulatory requirements will be completed, as applicable.*

Highly Effective Methods that are User Dependent

One of the acceptable barrier methods (described below) must be used in addition to the highly effective methods that are user dependent except for sexual abstinence.

1. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.
2. Progestogen-only hormone contraception associated with inhibition of ovulation.
3. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Acceptable Contraceptive Barrier Methods[a]

1. Male or female condom with or without spermicide[b]
2. Cervical cap, diaphragm, or sponge with spermicide
3. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)

a. Considered effective, but not highly effective methods - failure rate of ≥1% per year. Note that periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.

b. Male condom and female condom should not be used together (due to risk of failure with friction).

Collection of Pregnancy Information

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a participant or participant's partner becomes or is found to be pregnant during the participant's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a participant reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

CCI [redacted]

[redacted]

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Participants who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST OR ALT OR TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum sample for acetaminophen drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (LFT) abnormalities has yet been found. Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as Adverse Events (AEs)
• Marked sinus bradycardia (rate <40 beats per minute (bpm)) lasting minutes. • New PR interval prolongation >280 msec. • New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration. • Frequent premature ventricular contraction/complexes [per Abbreviations] (PVCs), triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as Serious Adverse Events (SAEs)

• QTcF prolongation >500 msec.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS >120 msec).
• New-onset right bundle branch block (QRS >120 msec).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptom-free patients with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
• Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (rate <40 bpm), accelerated idioventricular rhythm (40< x <100), and

monomorphic/polymorphic ventricular tachycardia >100 bpm (such as torsades de pointes).

- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as Serious Adverse Events

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

10.8. Appendix 8: Prohibited Concomitant Medications

This is not an all-inclusive list. Study personnel should stay current and consult with their pharmacy to exclude all concomitant medications that fall into the categories in the list below:

CYP1A2, CYP3A4, CYP2D6 Inhibitors (Moderate to Strong)

CYP 1A2
Ciprofloxacin
Clinafloxacin
Enoxacin
Fluvoxamine
Oltipraz
Rofecoxib
Zafirlukast

Etintidine
Idrocilamide
Methoxsalen
Mexiletine

Phenylpropanolamine
Pipemidic acid
Propafenone
Propranolol
Troleandomycin
Vemurafenib

CYP 2D6
Quinidine
Fluoxetine
Dacomitinib
Paroxetine
Buproprion

Cinacalcet
Terbinafine
Tipranavir
Moclobemide
Rolapitant
Mirabegron
Duloxetine
Eliglustat
Dronedarone

CYP1A2, CYP3A4, Inducers (Moderate to Strong)

CYP 1A2
Phenytoin
Rifampin
Ritonavir
Teriflunomide

MATE substrates with Narrow Therapeutic Index

Dofetilide

CYP1A2, CYP3A4, CYP2D6 Inhibitors (Moderate to Strong)	**CYP1A2, CYP3A4, Inducers (Moderate to Strong)**	**MATE substrates with Narrow Therapeutic Index**
CYP3A4	*CYP3A4*	
Viekira pak	Rifampin	
Indinavir	Mitotane	
Tipranavir	Avasimibe	
Ritonavir	Phenytoin	
Cobicistat	Carbamazepine	
Amiodarone		
Ketoconazole	Enzalutamide	
Troleandomycin	St. John's wort	
Telaprevir	Rifabutin	
Danoprevir	Phenobarbital	
Elvitegravir		
Saquinavir	Semagacestat	
Lopinavir	Efavirenz	
Itraconazole	Bosentan	
Voriconazole	Genistein	
Mibefradil	Thioridazine	
Clarithromycin	Nafcillin	
Posaconazole	Talviraline	
Telithromycin	Lopinavir	
Grapefruit Juice***, Marmalade	Modafanil	
Conivaptan	Etravirine	
Nefazodone	Lersivirine	
Nelfinavir		
Saquinavir		
Idelalisib		
Boceprevir		
Erythromycin		
Fluconazole		
Atazanavir		
Darunavir		
Diltiazem		
Dronedarone		
Crizotinib		
Aprepitant		
Casopitant		
Amprenavir		
Faldaprevir		
Imatinib		
Verapamil		
Netupitant		

CYP1A2, CYP3A4, CYP2D6 Inhibitors (Moderate to Strong)	**CYP1A2, CYP3A4, Inducers (Moderate to Strong)**	**MATE substrates with Narrow Therapeutic Index**
Nilotinib Tofisopam Cyclosporine Ciprofloxacin Isavuconazole Cimetidine		

- All prohibited drugs that are CYP1A2, CYP3A and CYP2D6 inhibitors require at least a 7 day or 5 half-lives (whichever is longer) prior to the first dose of study drug. Note: Amiodarone requires discontinuation at least 290 days (~5 half-lives, half-life averages ~58 days) prior to the first dose of IP.
- All prohibited drugs that are CYP1A2 and CYP3A inducers require at least a 28 day or 5 half-lives (whichever is longer) prior to the first dose of IP.
- ***It is recommended that subjects avoid excessive consumption of grapefruit juice exceeding 8 ounces (~240 mL) total in a day while in the study.
- **In a situation where appropriate medical care of a subject requires the use of a prohibited inhibitor or inducer:**

Moderate to potent inhibitors of CYP1A2, CYP3A and CYP2D6 and inducers of CYP1A2 and CYP3A are not permitted in the study EXCEPT in emergency situations requiring no more than one day of administration. ***Note: Amiodarone and mitotane are not permitted for any duration due to their long half-lives.*** Topical (including skin or mucous membranes) application of antimicrobial and antifungal medications is permitted.

10.9. Appendix 9: Columbia Suicide Severity Rating Scale (C-SSRS) for Screening and Baseline Visit

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ *Type # (1-5)* _____ *Description of Ideation* Past X Months - ***Most Severe Ideation:*** _____ *Type # (1-5)* _____ *Description of Ideation*	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

C-SSRS for any post-baseline visits "since last visit version":

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*) Past X Months - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐

Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐
Suicide:	**Yes No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

10.10. Appendix 10: Psoriasis Symptom Inventory (PSI) (Daily Assessment)

For each of the following questions, please mark (☑) the box of the one answer that best describes your experience.

In the questions below, the phrase "*skin lesions*" refers to the areas of your skin affected by your psoriasis.

For the following group of questions, the "**last 24 hours**" means from right now - back to yesterday at this same time.	**Not at all**	**Mild**	**Moderate**	**Severe**	**Very Severe**
1) Overall, during the last 24 hours, how severe was the **itch** from your psoriasis?					
2) Overall, during the last 24 hours, how severe was the **redness** of your skin lesions?					
3) Overall, during the last 24 hours, how severe was the **scaling** of your skin lesions?					
4) Overall, during the last 24 hours, how severe was the **burning** of your skin lesions?					
5) Overall, during the last 24 hours, how severe was the **stinging** of your skin lesions?					
6) Overall, during the last 24 hours, how severe was the **cracking** of your skin lesions?					
7) Overall, during the last 24 hours, how severe was the **flaking** of your skin lesions?					
8) Overall, during the last 24 hours, how severe was the **pain** you felt from your skin lesions?					

1 of 1

Psoriasis Symptom Inventory (PSI)-7 day

For each of the following questions, please mark (☑) the box of the one answer that best describes your experience.

In the questions below, the phrase "*skin lesions*" refers to the areas of your skin affected by your psoriasis.

For the following group of questions, the "**last 7 days**" includes today and the previous 6 days.	**Not at all**	**Mild**	**Moderate**	**Severe**	**Very Severe**
1) Overall, during the last 7 days, how severe was the **itch** from your psoriasis?					
2) Overall, during the last 7 days, how severe was the **redness** of your skin lesions?					
3) Overall, during the last 7 days, how severe was the **scaling** of your skin lesions?					
4) Overall, during the last 7 days, how severe was the **burning** of your skin lesions?					
5) Overall, during the last 7 days, how severe was the **stinging** of your skin lesions?					
6) Overall, during the last 7 days, how severe was the **cracking** of your skin lesions?					
7) Overall, during the last 7 days, how severe was the **flaking** of your skin lesions?					
8) Overall, during the last 7 days, how severe was the **pain** you felt from your skin lesions?					

10.11. Appendix 11: Peak Pruritus Numeric Rating Scale (PP-NRS)

Protocol ID: _____ CENTER | | | | | SUBJECT ID | | | | | | | | |

DATE OF VISIT | | - | | | | - | | | | |
dd MMM yyyy

Visit:

_____

PEAK PRURITUS-NRS

☐ (1) NOT DONE Language administered: ☒ (44) English for USA

On a scale of 0 to 10, with 0 being "no itch" and 10 being "worst itch imaginable", how would you rate your itch at the worst moment during the previous 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No itch										Worst itch imaginable

Simpson E, Beck L, Abhijit G, et al. Defining a responder on the Peak Pruritus Numerical Rating Scale (NRS) in patients with moderate-to-severe atopic dermatitis: Detailed analysis from randomized trials of dupilumab. J Am Acad of Dermatol 2017; 76:AB93.

Yosipovitch G, Reaney M, Mastey V, et al. Validation of the peak pruritus numerical rating scale: Results from clinical studies of dupilumab in adult patients with moderate to severe atopic dermatitis. J Am Acad of Dermatol 2017; 76:AB278.

CCI

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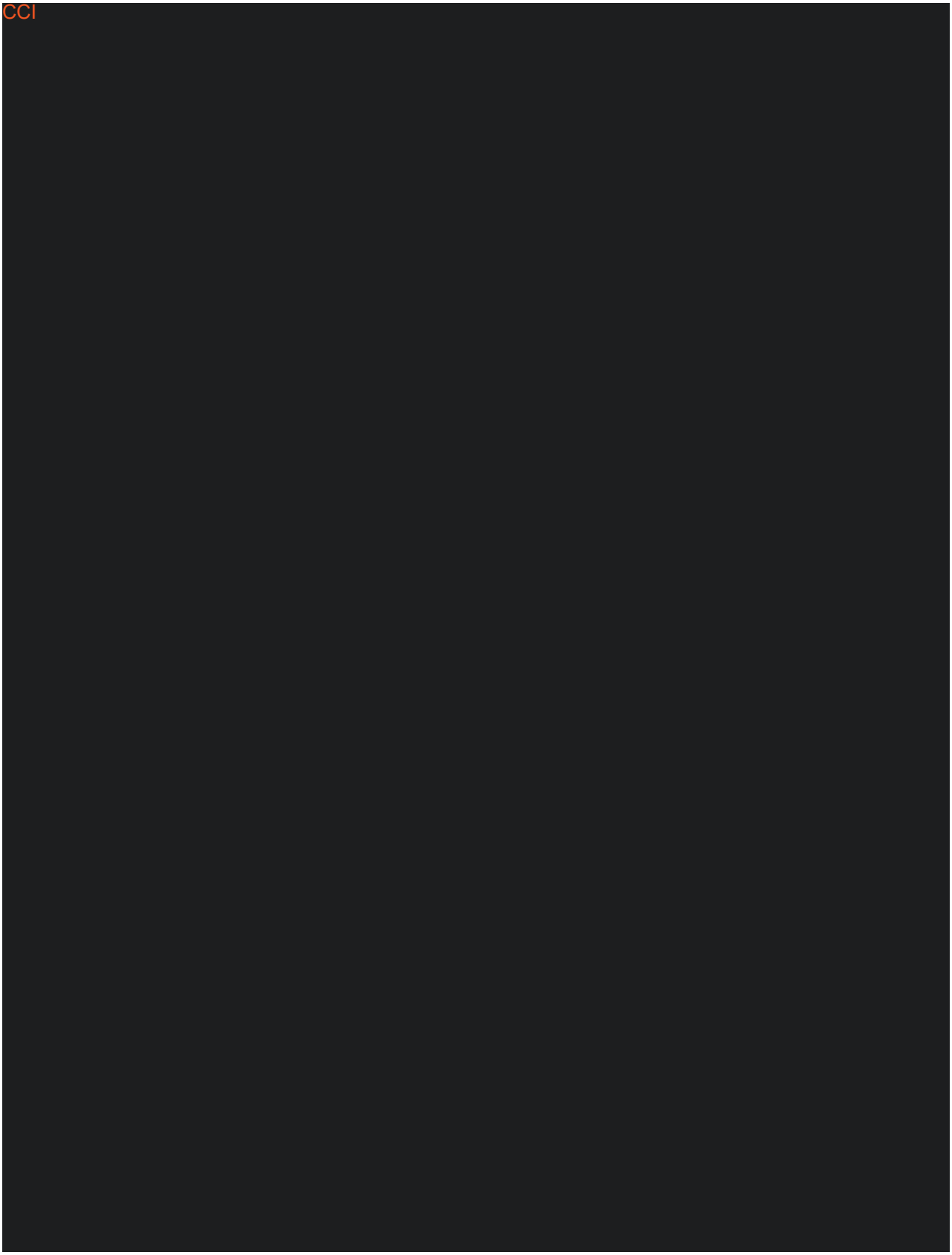

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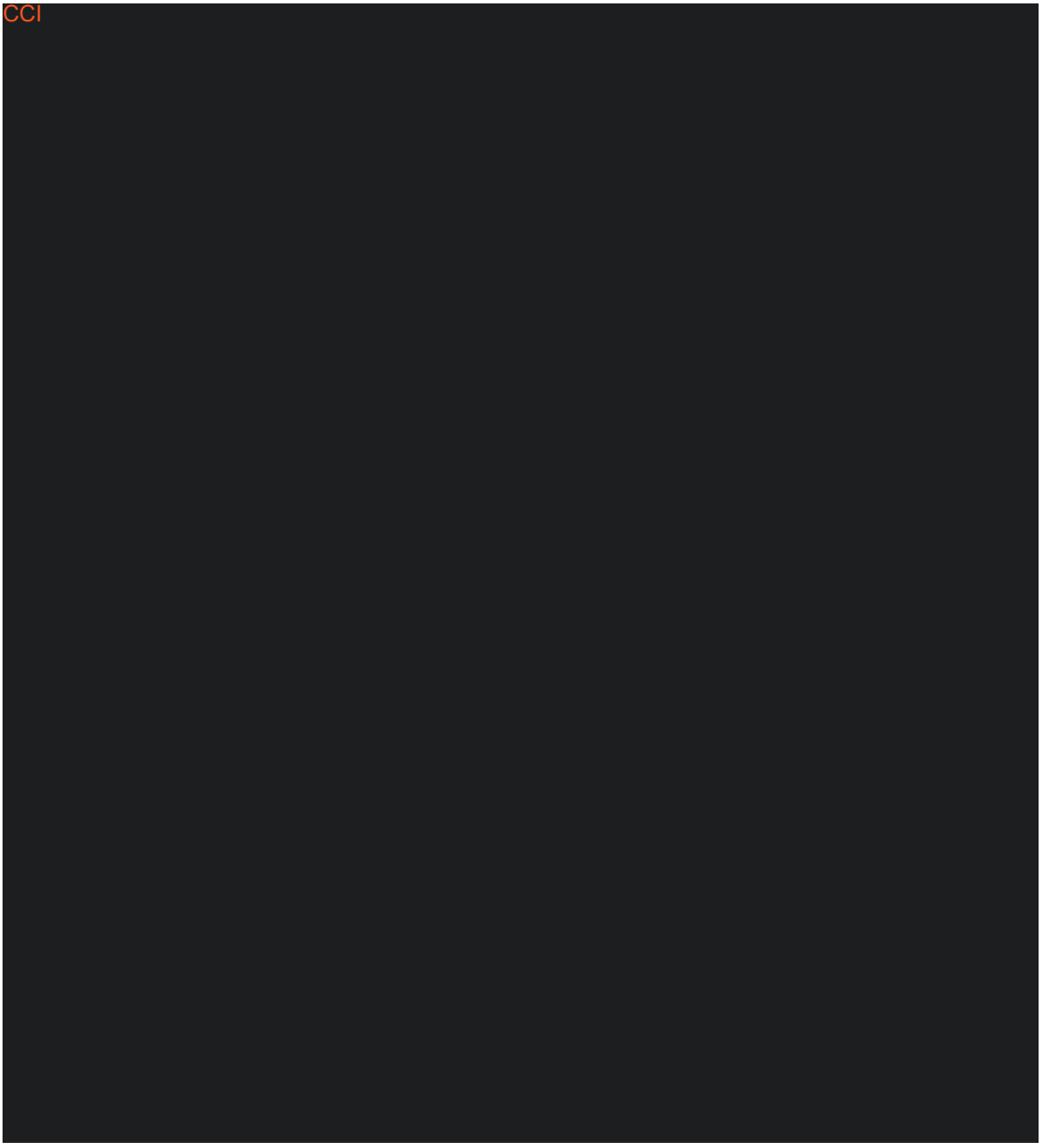

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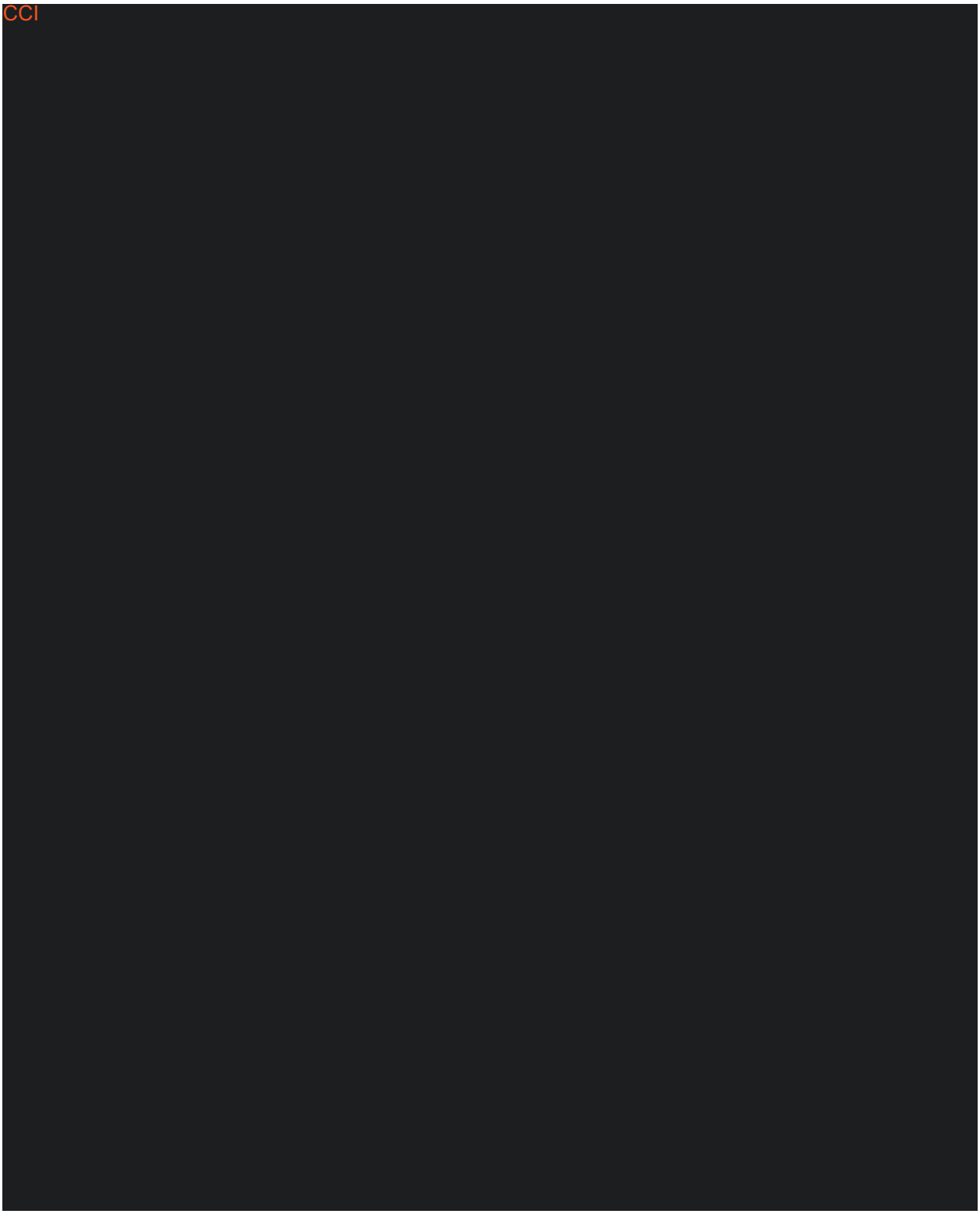

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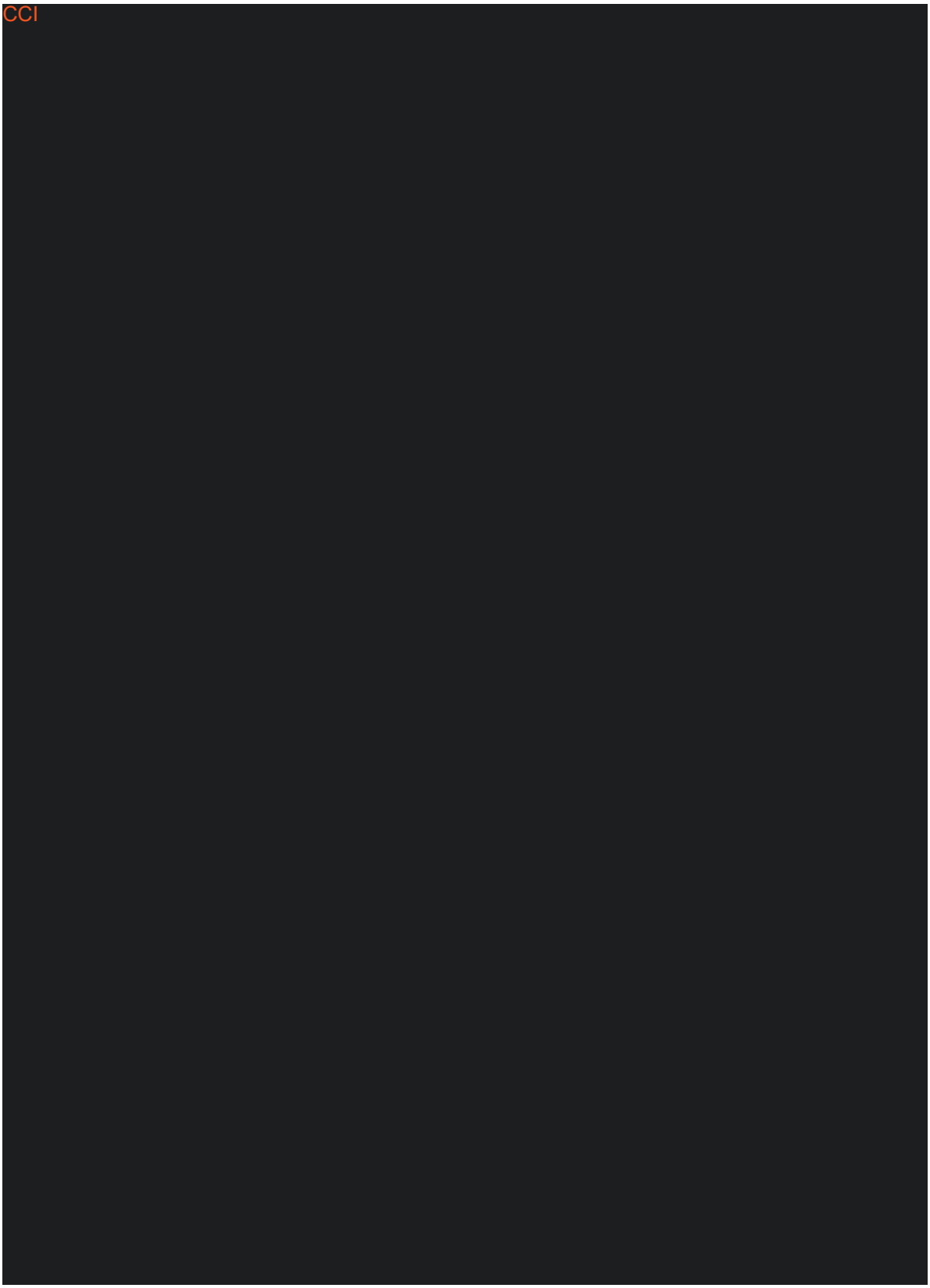


CCI

10.17. Appendix 17: Physician Global Assessment

ERYTHEMA (E)
Determine erythema (averaged over the whole body)
☐ 0 = no evidence of erythema (post-inflammatory hyperpigmentation and/or hypopigmentation may be present)
☐ 1 = light pink
☐ 2 = light red
☐ 3 = red
☐ 4 = dark, deep red

INDURATION (I)
Determine induration (averaged over the whole body)
☐ 0 = no evidence of plaque elevation
☐ 1 = barely palpable
☐ 2 = slight but definite elevation, indistinct edges
☐ 3 = elevated with distinct edges
☐ 4 = marked plaque elevation, hard/sharp borders

SCALING (S)
Determine scaling (averaged over the whole body)
☐ 0 = no evidence of scaling
☐ 1 = occasional fine scale
☐ 2 = fine scale predominates
☐ 3 = coarse scale predominates
☐ 4 = thick, coarse scale predominates

Add E + I + S = ⌊__⌋⌊__⌋ / 3 = ⌊__⌋.⌊__⌋⌊__⌋ (Total Average)

PHYSICIAN GLOBAL ASSESSMENT – based upon above Total Average
☐ 0 = Clear – cleared, except for any residual discoloration
☐ 1 = Almost Clear – majority of lesions have individual scores for E + I + S / 3 that averages 1
☐ 2 = Mild – majority of lesions have individual scores for E + I + S / 3 that averages 2
☐ 3 = Moderate – majority of lesions have individual scores for E + I + S / 3 that averages 3
☐ 4 = Severe – majority of lesions have individual scores for E + I + S / 3 that averages 4

Note: Total average is rounded to the nearest whole number score
eg, if total ≤2.49, score = 2; if total ≥2.50, score = 3

10.18. Appendix 18: eGFR Calculations

The estimated GFR (eGFR) will be calculated using the set of equations developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).

$CKD\text{-}EPI_{2009Scr}$

If female and serum creatinine (SCr) is ≤0.7 mg/dL:

- GFR (mL/min/1.73 m^2) = 144 x $(Scr/0.7)^{-0.329}$ x 0.993^{age} (x 1.159, if black).

If female and SCr is >0.7 mg/dL:

- GFR (mL/min/1.73 m^2) = 144 x $(Scr/0.7)^{-1.209}$ x 0.993^{age} (x 1.159, if black).

If male and SCr is ≤0.9 mg/dL:

- GFR (mL/min/1.73 m^2) = 141 x $(Scr/0.9)^{-0.411}$ x 0.993^{age} (x 1.159, if black).

If male and SCr is >0.9 mg/dL:

- GFR (mL/min/1.73 m^2) = 141 x $(Scr/0.9)^{-1.209}$ x 0.993^{age} (x 1.159, if black).

10.19. Appendix 19: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
Abs	Absolute
ADA	antidrug antibodies
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{24}	area under the concentration time curve from zero to 24 hours after single dose
AV	Atrioventricular
BA	Bioavailability
CCI	[redacted]
β-hCG	beta-human chorionic gonadotropin
BID	Two times per day
BMI	Body mass index
BP	blood pressure
bpm	beats per minute
CCI	[redacted]
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology
CL/F	apparent oral clearance
C_{max}	Total maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRO	contract research organization
CSA	clinical study agreement
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CT	clinical trial
DILI	drug-induced liver injury
CCI	[redacted]
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
EBV	epstein barr virus
EC	ethics committee
ECG	electrocardiogram

Abbreviation	Term
eCRF	electronic case report form
EDP	exposure during pregnancy
EE	ethinylestradiol
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EPO	epogen
ePRO	electronic patient reported outcomes
CCI [redacted]	[redacted]
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
FACS	Fluorescence-activated cell sorting
f_m	Fraction metabolized
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HBcAb	hepatitis B core antibody
HBsAB	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRQoL	Health related quality of life
HRT	hormone replacement therapy
CCI [redacted]	[redacted]
IB	investigator's brochure
IC50	50% inhibitory concentration
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IFN	interferon
IGRA	interferon gamma release assay
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP	investigational product
IP manual	investigational product manual
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device

Abbreviation	Term
IUS	intrauterine hormone-releasing system
IV	intravenous
IWR	interactive Web-based response
JAK	Janus kinase
LBBB	left bundle branch block
LAM	lactational amenorrhea method
LFT	liver function test
MAD	Multiple ascending dose
MATE1	multidrug and toxin extrusion protein
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDR1	multidrug resistant protein 1
MMR	Measles, mumps, rubella
MRI	Magnetic resonance imaging
MRP2	multidrug resistance-associated protein
msec	millisecond
N/A	not available
NIMP	noninvestigational medicinal product
CCI	[redacted]
NOAEL	no-observed-adverse-effect level
NTCP	sodium/taurocholate co-transporting polypeptide
OATP	organic anion transporting polypeptide
OC	oral contraceptives
OCT	organic cation transporter
PASI	Psoriasis Area and Severity Index
PCD	primary completion date
PCP	Primary care physician
PCR	Polymerase chain reaction
PD	pharmacodynamic(s)
PGA	Physicians global assessment
P-gp	P glycoprotein
PI	principal investigator
PK	pharmacokinetic(s)
PP-NRS	Peak-Pruritus Numerical Rating Scale
PR	Pulse rate
PRO	Patient reported outcome
PSI	Psoriasis symptom inventory
pSTAT	Phosphorylated signal transducer and activator of transcription
PT	prothrombin time
CCI	[redacted]
PUVA	Psoralen + UVA phototherapy
PVC	premature ventricular contraction/complex

Abbreviation	Term
QD	Once daily
QFT GIT	QuantiFERON TB Gold In Tube test
QFT G	QuantiFERONR TB Gold
QoL	Quality of Life
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
RBC	red blood cell
RNA	ribonucleic acid
SAD	Single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SCr	Serum creatinine
SDD	Spray dried dispersion
CCI [redacted]	[redacted]
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SToD	study team on demand
SUSAR	suspected unexpected serious adverse reaction
TB	Tuberculosis
TBili	total bilirubin
TEAE	Treatment emergent adverse event
TNF	Tumor necrosis factor
TYK2	tyrosine kinase 2
UGT	UDP-glucuronosyltransferase enzymes
ULN	upper limit of normal
US	United States
UVB	Ultraviolet band
Vss	Apparent volume of distribution at steady state
VTE	venous thromboembolic events
WBC	white blood cell
WOCBP	woman of childbearing potential

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