A PHASE 1, WITHIN COHORT, RANDOMIZED, DOUBLE BLIND, THIRD-PARTY OPEN, PLACEBO-CONTROLLED, SINGLE- AND MULTIPLE DOSE ESCALATION, PARALLEL GROUP STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF PF-06826647 IN HEALTHY SUBJECTS AND SUBJECTS WITH PLAQUE PSORIASIS

Investigational Product Number:	PF-06826647
Investigational Product Name:	Not Available (N/A)
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	N/A
Protocol Number:	C2501001
Phase:	1

[redacted]

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 3	05 April 2018	Section 1.3.2: updated the preliminary summary of clinical experience with PF-06826647. Sections 1.3.2 and 1.3.4.1: dose rationale updated with preliminary pharmacokinetic (PK) parameters and starting dose selection rationale for psoriasis cohorts. Section 3.1.1 and 3.1.2: introduction of optional cohort of Japanese subjects for PK comparability to support the clinical development plan for PF-06826647. Section 3.1.2: added text indicating that PF-06826647 dose level may be adjusted for the second psoriasis cohort based on emerging clinical data from the planned interim analysis, at the discretion of the Sponsor. Figure 1: Study Schematic updated with planned psoriasis cohort PF-06826647 dose level (based on recent psoriasis dose selection), dose level for the optional twice daily dose regimen cohort (BID), and optional Japanese cohort. Figure 2: legend updated to add optional Japanese cohort. Section 5.2: edits made to indicate that psoriasis cohorts will be sponsor-open, in order to allow sponsor review interim analysis results to inform dose decisions for psoriasis Cohort 2 PF-06826647 dose level. Section 4.1, Healthy Subject Inclusion Criteria: added single criterion for optional Japanese subject eligibility. Section 6.1: expanded the maximum duration of the screening period from 28 to 45 days for psoriasis subjects, in order to accommodate potential recruitment delays in between cohorts, while Sponsor reviews results from the interim

		analysis of psoriasis area and severity index scores. Section 7, Table 7: added creatine phosphokinase laboratory test to the chemistry panel for psoriasis subjects, to help ensure adequate safety monitoring for subjects receiving longer duration of treatment (ie, 28 days). Section 9.7: added interim analysis of key secondary PASI endpoint for the 400 mg psoriasis cohort, to be conducted when 21 subjects complete through study Day 28, to inform dose selection for subsequent psoriasis cohort and to support clinical development decisions for PF-06826647. Section 9.7: changed the planned psoriasis cohorts from sponsor blind to sponsor-open, in order to permit review of interim analysis results by a designated, limited number of sponsor colleagues to facilitate dose selection adjustment/decisions for psoriasis Cohort 2. Several administrative edits and minor clarifications made.
Amendment 2	20 December 2017	Schedule of Activities: Healthy Subject Single and Multiple Ascending Dose Periods. Added a blood sample collection on Day 8 of the single asending dose period, in order to adequately characterize the pharmacokinetic (PK) profile (terminal half-life) of PF-06826647. Removed a PK blood sample on Day 1, 16 hours post dose to avoid increasing blood volume requirements for subjects. Added a study visit on Day 17 for extended PK sample collection (with corresponding vital sign collection and adverse event monitoring), in order to adequately characterize the terminal half-life of PF-06826647. Removed the Day 1 and Day 10, 16 hour post-dose blood collection for PK assessment to avoid increasing blood volume requirements for subjects.

		The rationale for the above changes is based on emerging PK data from the C2501001 trial, which indicates that the terminal half-life of PF-06826647 may be dose dependent. The proposed PK sampling at approximately 168 hours post dose will help to fully characterize the PK profile of PF-06826647. Section 1.3.2: Updated the preliminary summary of clinical experience. Section 3.1.1 Study design- healthy subject single and multiple ascending dose period: extended the wash-out period between SAD and MAD dosing from 7 days to 14 days, based on preliminary assessment of the potential dose depenedent terminal half-life of PF-06826647. Section 3.1.1 and 3.2 – added language to the dose escalation paradigm to state that the highest dose to be tested in MAD will not exceed the highest dose tested in SAD cohort, and that he highest dose MAD cohort will commence if adequate safety is demonstrated in SAD cohort at the same or higher dose level and the projected exposure at steady state does not exceed NOAEL.
Amendment 1	06 November 2017	Various administrative changes. Schedule of activities: removed the Day 28 blood collection for viral surveillance from the multiple ascending dose period, added additional blood collection for pharmacokinetic (PK) assessment on Day 1. Schedule of activities: removed the Day 7 and Day 56 blood collection for viral surveillance from the Psoriasis Cohort schedule. CCI [redacted]

[redacted]

		CCI [redacted] Schedule of activities: added additional electrocardiogram (ECG) and vital sign assessment on Day 1 of the multiple ascending dose period, to coincide with the revised Day 1 PK collection. Section 1.3.2 Preliminary Summary of Clinical Experience added to provide rationale for revised PF-06826647 dose levels in the single and multiple ascending dose periods. Section 1.3.4 Updated Dose Rationale Based on Emerging Clinical Data added to provide rationale for revised PF-06826647 dose levels in the single and multiple ascending dose (MAD) periods. Section 3.1.1 Healthy Subject Single and Multiple Ascending Dose Periods, updated PF-06826647 dose levels based on emerging PK data from the C2501001 study, and added optional cohorts to further explore higher PF-06826647 exposure ranges. Figure 1 Study Schematic, updated to reflect amendment 1 PF-06826647 dose levels and addition of optional cohorts to further explore higher PF-06826647 exposure ranges. Section 4.6.1 Meals and Dietary Requirements, updated to specify revised meal requirements for the multiple ascending dose period and psoriasis cohorts (dosing with food based on the emerging PK data from Study C2501001). Section 5.5 Administration, harmonized with Protocol Section 4.6.1 to reflect the revised meal requirements for the trial. Section 6.1 Screening, updated screening window

		to allow eligible healthy subjects entry into the trial after lapse of the 28 day screening period, assuming study Day -1 paramters are within the limits of eligibility, as defined in Protocol Section 4. Section 7.10 Blood Volume, updated blood volume table to reflect reduced viral surveillance testing, and added PK sample collection on Day 1 of the MAD period. Section 7.11.1 CCI [redacted] clarified process for management of subjects at Screening visit, in accordance with site Institutional Review Board (IRB) request.
Original protocol	16 May 2017	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).

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections 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 schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

SCHEDULE OF ACTIVITIES Single Ascending Dose - Period 1: Healthy Subject Cohorts

Study Day ➡	**Screening -28 to -2**	**Day -1**	**Day 1**									**Day 2**		**Day 3**	**Day 4**	**Day 8[a] Follow-up /ET***
Hours Post Dose ➡ Protocol Activity ⬇			**0**	**0.5**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**24**	**36**	**48**	**72**	**168**
Randomization		X														
Informed Consent	X															
Admission to CRU		X														
Discharge from CRU															X	
Outpatient Visit[b]	X															X
Inclusion/Exclusion Criteria	X	X														
Drug/Alcohol/Tobacco History	X	X														
Medical History	X	X														
Physical Examination[c]	X	X														X
Demography	X															
Body weight	X	X														X
Height	X															
Interferon Gamma Release Assay (IGRA)	X															
HIV, HepBsAg, HepBcAb, HCVAb	X															
Blood Safety Labs (hematology & chemistry) (fasting)[d]	X	X										X			X	X
Fibrinogen		X										X				
Lipid Panel (fasting)[e]	X	X													X	X
Urinalysis	X	X										X		X	X	X
FSH[f]	X															

Study Day ➡	**Screening -28 to -2**	**Day -1**	**Day 1**									**Day 2**		**Day 3**	**Day 4**	**Day 8[a] Follow-up /ET***
Hours Post Dose ➡ Protocol Activity ⬇			**0**	**0.5**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**24**	**36**	**48**	**72**	**168**
Urine pregnancy test for females		X														X
Contraception Check[g]	X	X														X
Urine Drug Test	X	X														
ECG[h] (12-lead)	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Continous cardiac monitoring by Telemetry[i]		X	Monitored continuously through 8 hours post dose													
Vital signs: Supine single PR, BP, and Oral Temperature	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Viral Surveillance: [redacted]		C C I [redacted]					[redacted]									[redacted]
Study Treatment Administration			X													
PK Blood Sampling			X	X	X	X	X	X	X	X		X	X	X	X	X
Serious and non-serious adverse event monitoring		X	→	→	→	→	→	→	→	→	→	→	→	→		X
Prior/Concomitant treatments	X	X	→	→	→	→	→	→	→	→	→	→	→	→		X
Blood for mRNA analysis		X	X		X	X	X		X	X		X		X		
CCI [redacted]		[redacted]														

Abbreviations: →= ongoing/continuous event; BP = blood pressure; CCI [redacted] ;CRU = clinical research unit; CCI [redacted] ECG = electrocardiogram; FSH = follicle-stimulating hormone; CCI [redacted] ; HepBcAb = hepatitis B core antibody; HepBsAg = hepatitis B surface antigen; HCVAb = hepatitis C antibody; HIV = human immunodeficiency virus; CCI [redacted] ; PK = Pharmacokinetics; PR = pulse rate; CCI [redacted] .

a. End of study visit (±1 day).

b. Subjects will reside in the clinical research unit until the morning of Day 4 and return on Day 8 ±1 day for the end of the single dose period visit.

c. A full physical examination may be done at screening or may be differed to Day -1 (prior to randomization) of Period 1 at the discretion of the investigator. A limited physical exam may be completed on Day 8 (instead of a full exam) at the discretion of the investigator.

d. Chemistry and hematology labs are collected following fasting period of at least 8 hours (on Day 1, fasting applies to hour 0 labs only).

e. Lipid Panel (Cholesterol, Triglycerides, HDL, and LDLc): Fasting requirement of at least 8 hours.

f. FSH test to be performed at screening to confirm postmenopausal status in females who are amenorrheic for at least 12 consecutive months.

g. See protocol Section 4.6.4 (Contraception). Investigator will discuss appropriate contraception methods with male subjects.

h. ECGs will be collected in triplicate approximately 2-4 minutes apart except at screening and Day 8 where single ECG traces will be collected.

i. To establish a baseline, telemetry should be recorded for at least 2 hours before dosing. This may be done -2 hours immediately prior to dosing or at some 2 hour continuous interval in the 24 hours prior to dosing, as long as the recording is performed when the subject is awake. Continous cardiac monitoring will be conducted -15 minutes pre-dose through the 8 hour post dose period.

[redacted]

* ET: early termination – refer to Section 6.4 for additional guidance. If a subject is withdrawn due to an adverse event, in addition to the early termination assessments included in the schedule of activities, a final PK sample should be collected when possible.

Note: Time 0 on Day 1 is pre-dose. All assessments/samples at time 0 occur pre-dose, including PK sample collection.

SCHEDULE OF ACTIVITIES Multiple Ascending Dose - Periods 2: Healthy Subject QD and Optional BID and Japanese Subject Cohorts

The Schedule of Activities table provides an overview of the protocol visits and procedures.

Note: The below schedule assumes healthy subjects entering the multiple ascending dose (MAD) period have completed the single ascending dose period (SAD). Prior to entering the MAD period, any subjects that have not completed the SAD period must complete the screening assessments listed in the SAD Schedule of Activities (including sample collection for Pharmacogenomic Sample Prep D1), and must meet eligibility requirements for healthy subjects outlined in the Inclusion Criteria: Healthy Subject Single/Multiple Ascending Dose Cohorts.

Study Day ➡	**Day -1**	**Day 1**									**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**									**Day 11**	**Day 12**	**Day 13**	**Day 14**	**Day 17**	**Day 28[a] Follow-up /ET***
Hours Post Dose ➡ Protocol Activity ⬇		**0**	**0.5**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**24**								**0**	**0.5**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**24**	**48**	**72**	**96**	**168**	
Confirm key eligibility criteria are met (safety labs, vitals, ECG)[b]		X																													
Contraception Check[c]	X																														
Urine pregnancy test for females																															X
Admission to CRU	X																														
Discharge from CRU[d]																														X	
Outpatient visit																															X	X
Physical Examination[e]	X																														X
Body weight	X																														X
CCI	[redacted]										[redacted]					[redacted]			[redacted]												[redacted]
Blood Safety Labs (hematology & chemistry)(fasting)[f]	X[m]												X				X		X				X				X			X		X
Fibrinogen	X																											X				
Immunoglobulins: IgA, [redacted]	C C I																		[redacted]													[redacted]
[redacted]	[redacted]																		[redacted]													[redacted]
[redacted]	[redacted]																		[redacted]													[redacted]

Study Day ➡	**Day -1**	**Day 1**									**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**									**Day 11**	**Day 12**	**Day 13**	**Day 14**	**Day 17**	**Day 28[a] Follow-up /ET***
Hours Post Dose ➡ Protocol Activity ⬇		**0**	**0.5**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**24**								**0**	**0.5**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**24**	**48**	**72**	**96**	**168**	
Lipid Panel (fasting)[g]	X												X						X									X					X
Urinalysis	X											X			X		X		X		X	X		X				X				X
Urine Drug Test	X																															
ECG[h]	X	X		X	X	X	X		X		X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Vital signs: Supine single PR, BP and Oral Temperature[i]	X	X		X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
24 hr Urine Collection for CCI measurement, Creatinine Clearance, 6-β-Hydroxycortisol/cortisol ratio and Urine PK[j]	0-24 hr																		0-24 hr													
Study Treatment Administration		X									X	X	X	X	X	X	X	X	X													
PK Blood Sampling[k]		X	X	X	X	X	X	X	X		X		X		X		X		X	X	X	X	X	X	X	X		X	X	X	X	X
CCI																																
Serious and non-serious adverse event monitoring	X	X									→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X
Prior/Concomitant treatment	X	→									→	→	→	→	→	→	→	→	→									→	→	→	→	→	X
CCI																																

Abbreviations: →= ongoing/continuous event; BP = blood pressure; CCI ; CRU = clinical research unit; CCI ; ECG = electrocardiogram; CCI ; PK = Pharmacokinetics; PR = pulse rate; CCI

a. End of study procedures (±3 day).

b. Prior to dosing on Day 1, confirm that safety labs, ECG, and vital sign results, contraception check and prior/concomitant treatments from Day -1 (or from Day 8 of SAD if obtained within 48 hours of MAD Day -1) meet eligibility requirements outlined in Section 4.2. If labs, vitals, or ECG results are not within limits as outlined in Section 4.2, the site will notify sponsor. PI and sponsor will make the determination as to whether or not to allow the subject to continue into the MAD period. If the out of range values meet individual stopping rules outlined in the protocol, the subject will not continue into the MAD period.

c. See protocol Section 4.6.4 (Contraception). Investigator will discuss appropriate contraception methods with male subjects.

d. Subjects will reside in the clinical research unit until the morning of Day 14, returning on the morning of Day 28 ±3 days for the end of study procedures visit.

e. Limited physical examination (at the discretion of the principle investigator, exam may be limited or full).

f. Chemistry and hematology labs are collected following fasting period of at least 8 hours (on Day 10, fasting applies to hour 0 labs only).

g. Lipid panel (Cholesterol, Triglycerides, HDL, and LDLc):Fasting requirement of at least 8 hours.

h. ECGs will be collected in triplicate approximately 2-4 minutes apart on Days 1, 2, 4, 6, 8, 10 and Day 11. Single ECGs will be collected at all other specified visits.

i. Vitals taken on Day 1 will be performed prior to dosing and at approximately 2 hours post-dose; vitals taken on Days 2-9 will be performed approximately 2 hours post-dose; vitals taken on Days 12, 13, 14 will be performed in the morning. Vital signs will also be collected at the Day 17 and Day 28 (follow up/ET) visit.

j. An aliquot (urine blank) from the 0-24 hour period will be obtained from the urine collection for creatinine clearance on Day -1 for both the QD cohort and the BID cohort. On Day 10, urine will be collected for the BID cohort over 2 time intervals: 0-12 hours and 12-24 hours. The Day 10 PK sample will be obtained from the 0-12 hour interval.

k. Blood samples collected for PK pre-dose on Days 1, 2, 4, 6, 8 and 10, and on the morning of Days 11-14 (following at least a 8 hour fasting period, before breakfast) and on study Day 17.

C [redacted]
C
l [redacted]

* ET: early termination – refer to Section 6.4 for additional guidance. If a subject is withdrawn due to an adverse event, in addition to the early termination assessments included in the schedule of activities, a final PK sample should be collected when possible.

Note: An optional BID cohort may be included based on emerging PK data. Subjects participating in the BID cohort will follow the above schedule.

Administration of blinded study medication occurs on study Days 1 through 10. On study Days 1 through 9, all assessments listed occur pre-dose. On study Days 1 through 9, at 2 hours post dose, obtain vital signs including supine blood pressure, pulse rate (after at least 5 minutes of rest), and oral temperature. Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”. On study Day 10, the assessment time course depicted in the schedule of activities should be followed. Assessments on Day 10, hour 0, occur pre-dose.

SCHEDULE OF ACTIVITIES: Psoriasis Cohorts

Study Day ➡	Screening -28 to -2	D -1	D 1	D2	D 3	D 4	D 5	D 6	D 7	D 8	D 9	D 10	D 11	D 12	D 13	D 14	D 21	D 28									Day 29	D 35	D 42	D 56/ET[a]	D 84
Hours Post Dose ➡ Protocol Activity ⬇																		0	0.5	1	2	4	6	8	12	16	24				
Informed Consent	X																														
Drug/Alcohol/Tobacco History	X																														
Demography	X																														
Medical History	X																														
Prior/Concomitant treatment	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X
FSH[b]	X																														
Urine pregnancy test for females		X																												X	
Contraception Check[c]	X	X																										X	X	X	
Inclusion/Exclusion Criteria	X																														
Admission to CRU		X																													
Randomization		X																													
Discharge from CRU																											X				
Interferon Gamma Release Assay (IGRA)	X																														
Chest X-ray[d]	X																														
HIV, HepBsAg, HepBcAb, HCVAb	X																														
CCI [redacted]		[redacted]	[redacted]						[redacted]							[redacted]	[redacted]	[redacted]										[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]						[redacted]							[redacted]	[redacted]	[redacted]										[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]						[redacted]							[redacted]	[redacted]	[redacted]										[redacted]	[redacted]	[redacted]	[redacted]
Non lesional biopsy		X																													
Lesional biopsy of index lesion		X														X		X													

[redacted]

Study Day ➡	Screening -28 to -2	D -1	D 1	D2	D 3	D 4	D 5	D 6	D 7	D 8	D 9	D 10	D 11	D 12	D 13	D 14	D 21	D 28									Day 29	D 35	D 42	D 56/ET[a]	D 84
Hours Post Dose ➡ Protocol Activity ⬇																		**0**	**0.5**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**24**				
Clinical Evaluation: Plaque Lesion Photography[f]		X							X							X		X											X	X	X
CCI [redacted]		[redacted]																													
Outpatient visit																												X	X	X	X
Physical Examination[g]	X								X							X	X	X												X	
Body weight	X																	X												X	
Height	X																														
CCI [redacted]		[redacted]							[redacted]							[redacted]		[redacted]												[redacted]	
		[redacted]							[redacted]							[redacted]		[redacted]												[redacted]	
Blood Safety Labs (chemistry and hematology) (fasting)[h]	X	X				X		X		X		X				X	X	X					X					X	X	X	
CCI [redacted]		[redacted]																[redacted]												[redacted]	
		[redacted]																[redacted]												[redacted]	
		[redacted]																[redacted]												[redacted]	
Lipid Panel (fasting)[i]	X	X								X						X	X	X												X	
Urinalysis	X	X			X			X				X				X	X	X		X	X	X	X							X	
Urine Drug Test	X	X																													
ECG[j]	X		X						X		X				X	X	X	X	X	X	X		X				X			X	
Vital signs: Supine single PR, BP and Oral Temperature[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study Treatment Administration[l]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X													
PK Blood Sampling[m]			X						X							X	X	X	X	X	X	X	X	X	X	X	X	X			
CCI [redacted]		[redacted]														[redacted]		[redacted]													
		[redacted]														[redacted]		[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]			[redacted]	
		[redacted]														[redacted]		[redacted]											[redacted]		

Study Day ➡	Screening -28 to -2	D -1	D 1	D2	D 3	D 4	D 5	D 6	D 7	D 8	D 9	D 10	D 11	D 12	D 13	D 14	D 21	D 28									Day 29	D 35	D 42	D 56/ET[a]	D 84
Hours Post Dose ➡ Protocol Activity ⬇																		0	0.5	1	2	4	6	8	12	16	24				
CCI																															
Serious and non-serious adverse event monitoring		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X
CCI																															
CCI																															
Patient Global Assessment			X						X							X	X	X												X	X
CCI																															
PHQ-8[o]	X																														
SBQ-R[o]	X																														
CCI																															

Abbreviations: →= ongoing/continuous event; CCI ; BP = blood pressure; CCI ; CRU = clinical research unit; D=Day; CCI ; ECG = electrocardiogram; CCI ; FSH = follicle stimulating hormone; HepBcAb = hepatitis B core antibody; HepBsAg = hepatitis B surface antigen; HCVAb = hepatitis C antibody; HIV = human immunodeficiency virus; CCI ; IGRA = interferon gamma release assay; CCI PK = Pharmacokinetics; PR = pulse rate; CCI

a. End of study procedures (±3 days). Note: the visit window (±3 days) applies to outpatient visits on study Days 35, 42, 56, and 84. ET: early termination – refer to Section 6.4 for additional guidance. If a subject is withdrawn due to an adverse event, in addition to the early termination assessments included in the schedule of activities, a final PK sample should be collected when possible.

b. FSH test to be performed at Screening to confirm postmenopausal status in females who are amenorrheic for at least 12 consecutive months.

c. See protocol Section 4.6.4 (Contraception). Investigator will discuss appropriate contraception methods with male subjects.

d. Only required for psoriasis subjects with history of previously (adequately) treated TB, as described in the protocol eligibility criteria (see protocol Section 4.3). Chest x-ray taken within 3 months of screening visit can be used to assess eligibility if available.

C [redacted]
C

f. Target lesion and regional photography.

g. A full physical examination may be done at screening or may be differed to Day -1 (prior to randomization) at the discretion of the investigator. A full physical exam should also be performed at Day 28. A limited physical exam can be performed at all other times if no findings during previous examination or new/open AE, at the discretion of the investigator.

h. Safety labs (chemistry and hematology) are collected following at least 8 hours of fasting (on Day 28, fasting requirement applies to hour 0 only).

i. Lipid panel (Cholesterol, Triglycerides, HDL, and LDLc): Fasting requirement of at least 8 hours.

j. Triplicate ECGs will be collected on Day 1, Day 28, and Day 29. Single ECGs will be collected at all other time points/visits.

k. Vitals taken on Days 1-28 will be performed at approximately 2 hours post-dose; vitals will also be taken on Day 29, 35, 42 and 56/ET (follow-up) visits.

l. Study treatment administration occurs once daily for 28 days, starting on Day 1 and ending on Day 28.

m. Blood samples collected for PK predose on Days 1, 7, 14, 21, and 28 (time 0), and on the morning of Day 29 and Day 35.

C [redacted]

o. Subjects who have recent or active suicidal ideation or behavior will be excluded from the study (refer to Section 4.4).

C [redacted]

Administration of blinded study medication occurs on study Days 1 through 28. On study Days 1 through 21, all assessments listed in the schedule of activities occur pre-dose. On study Days 1 through 21, at 2 hours post dose, obtain vital signs including supine blood pressure, pulse rate (after at least 5 minutes of rest), and oral temperature. Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”. On study Day 28, the assessment time course depicted in the schedule of activities should be followed. Assessments on Day 28, hour 0, occur pre-dose.

1. INTRODUCTION

The Janus kinase (JAK) family, including JAK1, JAK2, JAK3 and Tyrosine kinase 2 (TYK2), is a group of cytoplasmic tyrosine kinases that mediate signal transduction via interactions with Type 1 and Type 2 cytokine receptors critical for leukocyte activation, proliferation, survival and function.[5,6]

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

This single- and multiple-ascending dose study is the first evaluation of PF-06826647 in humans. The goal is to assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) in healthy subjects and subjects with plaque psoriasis. The inclusion of a psoriasis cohort will facilitate optimal assessment of TYK2 modulation in vivo, given that Th1 and Th17 pathways are not up regulated in the absence of inflammation.

1.1. Mechanism of Action/Indication

PF-06826647 is a TYK2 inhibitor that is currently being developed for the treatment of psoriasis and Crohn's disease (CD).

TYK2 pairs with JAK1 to mediate type I interferon (IFN) signaling and with JAK2 to transmit interleukin (IL-12) and IL-23 signaling. Additionally JAK1 pairs with JAK3 to mediate γ-common cytokine signaling and also with JAK2 and/or TYK2 to transmit the signals of additional cytokines important in inflammation and immune responses including IL-6, and IFNγ, JAK2 homodimers are critical for the signaling of hematopoietic cytokines and hormones including erythropoietin (EPO), IL-3, granulocyte-macrophage colony-stimulating factor (GM-CSF) and prolactin. Key cytokines implicated in the pathophysiology of both Crohn's disease and plaque psoriasis, such as IL-12 and IL-23, require TYK2 for signal transduction, indicating that inhibition of TYK2 mediated signaling could be efficacious in the treatment of these inflammatory conditions.

1.2. Background

1.2.1. Binding to the Pharmacological Target

PF-06826647 is an inhibitor of human TYK2. The inhibitory potency of PF-06826647 on human TYK2 was determined by using a mobility shift microfluidic assay to monitor phosphorylation of a synthetic peptide by recombinant human TYK2. When the assay was performed under 1 mM adenosine triphosphate (ATP), PF-06826647 showed IC_{50} (half maximal inhibitory concentration) of 14.9 nM against human TYK2. PF-06826647 was less active against human JAK1, JAK2 and JAK3, with IC_{50}s of 383, 74.2 and >10,000 nM, respectively, at 1 mM ATP using the same assay technology. PF-06826647 is less potent against mouse TYK2 in the kinase assays. Sequence alignment of the TYK2 enzyme reveals that, within the ATP binding pocket, human TYK2 has an isoleucine at amino acid 960,

while other species with known sequences bear a valine at the equivalent position, except in chimpanzee. Mouse TYK2 and human TYK2 I960V mutant kinase domains were prepared to gain an understanding of species selectivity, relative to the wild-type human protein. The IC_{50} of PF-06826647 measured in this assay at 1 mM ATP was 385 nM for mouse TYK2, and 344 nM for human TYK2 I960V mutant. The results indicate that PF-06826647 binds more strongly to TYK2 with isoleucine at amino acid 960 than valine, and resulting in relatively lower potency in preclinical species when compared to human.

1.2.2. Cellular Potency and Selectivity

The JAK family kinases mediate signal transduction via interactions with type I (eg, IL-2, IL-6, IL-23, GM-CSF) and type II (eg, type I IFNs, IL-10) cytokine receptors. The JAK signaling pathways involves various hetero- or homodimer combinations (TYK2/JAK2, JAK1/JAK3, JAK1/JAK2, TYK2/JAK1, or JAK2/JAK2). Upon binding of the cytokine to its receptor, the associated JAKs are activated, and phosphorylate each other and the receptor. The phosphorylated receptors serve as docking sites for the signal transducer and activator of transcription (STAT) family (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6) of transcription factors. The STATs are then phosphorylated by the co-localized JAKs, which stabilizes homo- or heterodimeric STAT complexes that translocate to the nucleus where they bind to specific gene promoters and modulate transcription of a range of target genes.

The cellular potency and selectivity of PF-06826647 was mainly evaluated using human whole blood (HWB). HWB was pretreated with PF-06826647 and challenged with various cytokines to stimulate phosphorylation of STATs. Inhibition of STAT phosphorylation by PF-06826647 was measured by flow cytometry using intracellular staining with specific phospho-STAT antibodies.

IL-12 and IL-23, both signaling through JAK2/TYK2, are important for the differentiation of Th1 and Th17, respectively. Treatment of HWB with PF-06826647 led to inhibition of IL-12 induced STAT4 phosphorylation with an IC_{50} of 53 nM and IL-23 induced STAT3 phosphorylation with an IC_{50} of 112 nM. In human peripheral blood mononuclear cells (PBMCs), PF-06826647 potently inhibited IL-12 induced pSTAT4 with an IC_{50} of 20 nM.

Treatment of HWB or human PBMCs with PF-06826647 resulted in inhibition of IFNα stimulated STAT3 phosphorylation (mediated via TYK2/JAK1) with an IC_{50} of 66 nM and 23 nM, respectively. Although IL-10 signaling is also mediated via the TYK2/JAK1 pair, PF-06826647 was less potent against IL-10 induced STAT3 phosphorylation with an IC_{50} of 427 nM in HWB. Signaling of the type II interferon, IFNγ, is controlled by JAK1/JAK2. PF-06826647 was shown to block IFNγ induced pSTAT1 with an IC_{50} of 2,220 nM in HWB.

The common γ chain cytokines, such as IL-15 and IL-21, are dependent on JAK1 and JAK3 to initiate signaling upon binding of their receptors. PF-06826647 pre-incubation in human whole blood resulted in an inhibition of STAT5 phosphorylation induced by IL-15 with an IC_{50} of 4,840 nM and an inhibition of STAT3 phosphorylation induced by IL-21 with an IC_{50} of 4,890 nM in lymphocytes.

IL-6 signaling is thought to be dependent on JAK1/JAK2/TYK2. The IC_{50} values in the IL-6 assays were dependent on the STAT phosphorylated. For example, IL-6 stimulated STAT1 phosphorylation (IC_{50} = 566 nM) was more readily inhibited than STAT3 phosphorylation (IC_{50} = 4,370 nM) by PF-06826647 in $CD3^+$ lymphocytes of human whole blood. IL-27 signaling is also mediated by the same JAK complex as IL-6. PF-06826647 suppressed IL-27 induced pSTAT3 with an IC_{50} of 201 nM.

IL-4 initiates signal transduction through one of two different receptor complexes, a type I receptor expressed on hematopoietic cells or a type II receptor expressed mainly on non-hematopoietic cells. The type I receptor is a heterodimer of IL-4 receptor (IL-4R) α and the γc chain, and the type II receptor is a heterodimer of IL-4Rα and IL-13 receptor (IL-13R) α1. IL-13 only activates the type II IL-4R. Following cytokine binding, the type I receptor (IL-4Rα and the γc chain) activates JAK1 and JAK3, while the type II receptor (IL-4Rα and IL-13Rα1) stimulates mainly JAK1. Activation of either type I or type II receptors leads to phosphorylation of STAT6. In $CD20^+$ B and $CD3^+$ T cells, IL-4-induced pSTAT6, mediated via JAK1 and JAK3, was inhibited by PF-06826647 with IC_{50} values of 3,413 nM and 1,227 nM, respectively. In $CD14^+$ monocytes, PF-06826647 showed an IC_{50} value of 568 nM against IL-4 induced pSTAT6, which is controlled mainly by JAK1. In HWB, IL-13 induced pSTAT6 was detected in $CD14^+$ monocytes and $CD20^+$ B cells, but not in $CD3^+$ T cells. PF-06826647 pre-incubation in human whole blood resulted in an inhibition of STAT6 phosphorylation induced by IL-13 with IC_{50} values of 807 nM and 393 nM detected in $CD14^+$ monocytes and $CD20^+$ B cells, respectively.

Inhibition of JAK2/JAK2 homodimer was assessed through erythropoietin (EPO) induced STAT5 phosphorylation with an IC_{50} of 547 nM in human bone marrow $CD34^+$ progenitor cells spiked into human whole blood. PF-06826647 maintains a 10-fold selectivity over JAK2 as determined by comparing inhibition of JAK2 dependent EPO signaling in bone marrow $CD34^+$ progenitor cells to the TYK2/JAK1dependent human whole blood IFNα assay. These results demonstrate that PF-06826647 potently inhibits TYK2-dependent signaling pathways, while showing modest suppression of the JAK2/JAK2 driven pathway.

PF-06826647 was also assessed for its cellular activity in various cell types and settings. IL-12 is a critical cytokine that is required for the promotion of Th1 development as well as IFNγ production. IL-12 synergizes with IL-18 in inducing IFNγ production. IL-12 and IL-18 activate different transcriptional factors: the former activates STAT4, and the latter activates NF-κB and AP-1, which signaling is independent of the JAK family kinases. IL-12 upregulates expression of the IL-18 receptor to promote IL-18-driven signaling, and IL-12-activated STAT4 enhances the binding activity of IL-18-induced AP-1 to IFNγ promoter.

PF-06826647 was tested for its inhibitory activity against IFNγ production which was triggered by a combination of IL-12 and IL-18 in human $CD4^+$ T, $CD8^+$ T, and $CD56^+$ NK cells. IL-12 signals via TYK2 and JAK2. As expected, PF-06826647 abrogated IFNγ production by blocking the IL-12 signaling that was necessary for the synergy of IL-12 and IL-18. The inhibition by PF-06826647 was dose dependent with IC_{50} values of 177, 123, and 217 nM in human $CD4^+$ T, $CD8^+$ T, and $CD56^+$ NK cells, respectively.

Type I IFNs have been shown to contribute to the progression of many autoimmune diseases. Numerous gene expression profiling studies have shown up-regulation of interferon induced genes. In vitro, type I IFN release and the resulting gene expression pattern can be induced in PBMC using immune complexes constructed artificially by combining immunoglobulin G (IgG) purified from systemic lupus erythematosus patients with apoptotic cellular debris from U937 cells as a source of nuclear antigens. The in vitro activity of PF-06826647 inhibiting type I IFN induced genes in normal human PBMC stimulated with immune complexes was assessed.

IC_{50} curves were generated in PBMCs from 3 human volunteer blood donors for IFN induced genes quantified by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR). PF-06826647 potently blocked immune complex induced expression of 3 IFN induced genes, radical S-adenosyl methionine domain-containing protein 2 (RSAD2), ubiquitin specific peptidase 18 (USP18) and guanylate binding protein 1 (GBP1) with IC_{50}s of 36.7, 44.1, and 43.8 nM, respectively.

In summary, PF-06826647 potently inhibited TYK2-dependent cytokine receptors, such as receptors for IFNα, IL-12 and IL-23, with selectivity against receptors that do not signal through TYK2, like receptors for IL-15 (signaling through JAK1/JAK3), IFNγ (signaling through JAK1/JAK2) or EPO (signaling through JAK2/JAK2).

1.2.3. Non-Clinical Pharmacokinetics and Metabolism

Single dose pharmacokinetic studies with PF-06826647 were conducted after oral and 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 CYP450 mediated metabolism through CYP1A2, 2D6 and 3A. PF-06826647 did not inhibit the major cytochrome CYP450 or UGT enzymes (IC_{50} >25 μM). PF-06826647 induced CYP3A4 messenger Riboneucleic 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.

Human pharmacokinetics of PF-06826647 were predicted using physiologically based pharmacokinetic modeling, scaling intrinsic clearance from human liver microsomes and hepatocytes. Human blood clearance is predicted to be ~2 mL/min/kg, volume of distribution 1.3 L/kg, half-life 6 hours, and oral bioavailability of ~90%. The once daily clinical dose predicted to achieve the average concentration resulting in approximately 80% inhibitory effect ($C_{av80,}$ss) on IL-12 is 20 mg. The target unbound $AUC_{24,ss}$ to achieve an 80% average daily inhibition of IL-12 (TYK2/JAK2) is approximately 587 ng*h/mL. The corresponding PF-06826647 unbound C_{max} is approximately 52 ng/mL (135 nM).

1.2.4. Non-clinical Safety Studies

PF-06826647 potently inhibited kinase activity of human TYK2 with relative selectivity over JAK1, JAK2 and JAK3 of ≥5x, as well as good specificity profile over the broader kinome. PF-06826647 blocked various TYK2-dependent cellular functions in vitro, including phosphorylation of STAT induced by TYK2-dependent cytokines such as IFNα, IL-12 and IL-23, with selectivity against TYK2-independent cytokines like IL-15 (JAK1/JAK3 dependent), IFNγ (JAK1/JAK2 dependent) or EPO (JAK2/JAK2 dependent) in HWB, IL-12-induced IFNγ production in human T and NK cells, and type I IFN gene signature induced by immune complexes in human PBMCs. Treatment with PF-06826647 significantly suppressed imiquimod induced skin inflammation in a mouse model as measured by ear thickness, gene expression of many inflammatory mediators, and induction of IL-17A and pSTAT3, demonstrating the in vivo anti-inflammatory effects of PF-06826647.

PF-06826647 was profiled in vitro against a broad panel of receptors, kinases, transporters, ion channels, enzyme targets (at 10,000 nM), and phosphodiesterases (at ≤30,000 nM). A ≥50% inhibition was observed against Abl, AurA/Aur2, KDR (VEGFR2), and Src kinases with IC_{50} values of 1300, 710, 160, and 4300 nM, respectively. These IC_{50} values correspond to approximately 9.6x, 5.3x, 1.2x, and 32x, respectively, the predicted human efficacious unbound C_{max}. In a functional cell-based assay, PF-06826647 inhibited Abl and VEGFR2 kinase less potently with IC_{50} values of >30,000 nM and 18,000 nM which are >222x and 133x the projected human efficacious unbound C_{max}, respectively. These results indicate that PF-06826647 has little potential for off-target pharmacology.

In safety pharmacology studies, PF-06826647 had no effect on the neurofunctional or pulmonary systems in rats up to the highest dose tested (500 mg/kg). The unbound C_{max} at 500 mg/kg is 34x the predicted human steady-state unbound C_{max} at a projected human efficacious dose of 20 mg.

In pivotal cardiovascular safety pharmacology and 1-month repeat-dose toxicity studies in cynomolgus monkeys, no PF-06826647-related changes were observed in any cardiovascular parameter measured up to the highest dose tested (300 mg/kg), corresponding to approximately 28x the projected human efficacious unbound C_{max}. In an exploratory cardiovascular safety pharmacology study in rats, PF-06826647-related increased diastolic and mean blood pressure (each +3 mmHg) from 0-2 hours postdose, and increased heart rate (+18 to +13 bpm) from 2-12 hours postdose, were observed at 500 mg/kg (the highest dose tested). No PF-06826647-related effects were observed in any parameter measured at ≤50 mg/kg, corresponding to 6.5x the predicted human efficacious unbound C_{max}.

The hERG IC_{50} for PF-06826647 was >10,000 nM, which is >74x the predicted human efficacious unbound C_{max}.

PF-06826647 was negative for mutagenicity in the GLP bacterial reverse mutation assay. Although PF-06826647 was positive in the in vitro micronucleus assay in TK6 cells by an aneugenic mechanism, it did not induce micronuclei in vivo in reticulocytes in the 1-month study in rats (at exposures 41x the predicted human unbound efficacious C_{max} and AUC_{24}).

PF-06826647 absorbs in the ultraviolet A (UVA) and ultraviolet B (UVB) range and could present potential risk for phototoxicity. Therefore, PF-06826647 will be evaluated for phototoxicity prior to enrollment in large clinical trials.

PF-06826647 was evaluated in rats and cynomolgus monkeys in single- and repeat-dose toxicity and/or toxicokinetic studies up to 1 month in duration. The high dose selection in the 1-month pivotal study was based on observed exposure plateau in exploratory studies. Target organs and systems identified with PF-06826647 administration in rats and monkeys include the immune and hemolymphatic systems (thymus, spleen, lymph nodes, bone marrow, erythron, and leukon), bone, and liver. In addition, other PF-06826647-related findings occurred in clinical observations, body weights, and/or clinical pathology parameters. In the immune and hemolymphatic system, decreased lymphoid cellularity within the lymphoid follicles of the thymus and spleen was observed in rats ≥30 mg/kg/day, and in the thymus,

spleen, and lymph node (mesenteric) in monkeys at ≥150 mg/kg/day. This finding was associated with nondose-related lower or decreased lymphocyte, white blood count (WBC), and/or eosinophil counts in rats and monkeys at ≥30 mg/kg/day. Additionally, lower reticulocyte numbers were observed in rats at ≥30 (15 twice a day (BID) mg/kg/day and not associated with any adverse effects in red blood cell (RBC) mass parameters. Further observations included lower numbers of T cells, B cells, NK cells, and absolute lymphocyte counts in peripheral blood and/or spleen of rats at ≥30 (15 BID) mg/kg/day for cytotoxic T cells and NK cells in spleen or ≥200 (100 BID) mg/kg/day for all other PF-06826647-related immunophenotyping parameters. In monkeys, decreased numbers of T cells in peripheral blood and NK cells in peripheral blood and spleen occurred at ≥30 mg/kg/day, and decreased number of T cells, B cells, and absolute lymphocytes occurred in the spleen at 300 mg/kg/day. Minimal decreased cellularity in all cell lineages was observed in the bone marrow (sternum) of monkeys at ≥150 mg/kg/day and corresponded with decreased RBC mass parameters (red blood cell (RBC), hemoglobin (HGB), and hematocrit (HCT)), reticulocytes, and WBC counts at ≥30 mg/kg/day. The findings in the thymus, spleen, lymph nodes, bone marrow, erythron, and leukon observed in rats and monkeys are consistent with the pharmacological activity of PF-06826647, and were not adverse due to their low magnitude/severity of the effects and/or because they were not associated with any clinical or microscopic evidence suggestive of PF-06826647-related infections in these animals.

PF-06826647-related higher or increased alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and/or triglycerides were observed in rats at ≥30 (15 BID) mg/kg/day and in monkeys at ≥30 mg/kg/day. Additionally, higher cholesterol was observed in rats at 500 (250 BID) mg/kg/day. None of these alterations were adverse due to their minor magnitude and the absence of correlating microscopic findings.

PF-06826647-related nonadverse minimally higher femoral metaphyseal medullary trabecular bone thickness was observed in the bone of the stifle joint in rats at 500 mg/kg/day after 14 days of repeated administration, but not at the same dose in the 1-month study. The growth plate was within normal limits, and no evidence of inflammation, necrosis, or hemorrhage of the medullary trabecular bone was noted. This effect on bone was not observed in monkeys.

Other nonadverse PF-06826647-related findings included clinical observations, body weights, and/or clinical pathology parameters that lacked in-life or post-mortem correlates and/or were minor in magnitude. These included higher mean fibrinogen in rats at ≥200 (100 BID) mg/kg/day; higher mean total protein, consisting of both higher mean albumin and globulin, in rats at 500 (250 BID) mg/kg/day; dose-dependent, lower mean body weight gain and mean absolute body weight in rats at ≥30 (15 BID) mg/kg/day; decreased phosphorus in monkeys at ≥30 mg/kg/day; and pale/white discolored feces in monkeys at ≥100 mg/kg/day.

The no-observed-adverse-effect-level (NOAELs) in the 1-month pivotal rat and monkey toxicity studies were 500 (250 BID) mg/kg/day in rats (unbound C_{max} = 1870 ng/mL and AUC_{24} = 16,600 ng•h/mL) and 300 mg/kg/day in cynomolgus monkeys (unbound C_{max} = 1790 ng/mL and AUC_{24} = 19,900 ng•h/mL). Exposures at these doses were 28x to 36x the predicted human efficacious unbound exposures (C_{max} and AUC_{24}).

The nonclinical safety profile of PF-06826647 has been adequately characterized to support progression into clinical trials of up to 4 weeks

1.2.5. Biopharmaceutics Properties

PF-06826647 is a basic compound. The cLogP and permeability, as measured in cell lines, indicate that the molecule should readily permeate the intestinal membrane. The solubility will be low across the physiological pH. PF-06826647 has been formulated as a spray dried dispersion to improve solubility, and has shown improved bioavailability as compared to crystalline PF-06826647 in preclinical species. Based on preclinical exposure data and modeling, we expect PF-06826647, formulated as a spray dried dispersion, to be moderately to well absorbed at the predicted dosing range in the first in human (FIH) study using a suspension or immediate release (IR) tablet of the spray dried dispersion.

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the Investigators Brochure (IB).

1.3. Rationale

1.3.1. Study Rationale

This Phase 1 first-in-human (FIH) study will evaluate safety, tolerability, PK and CCI of PF-06826647 in healthy subjects and in subjects with plaque psoriasis. The combined single ascending dose (SAD) and multiple ascending dose (MAD) design was selected because it provides the opportunity to shorten the time between completion of the SAD and MAD phases of early drug development, without compromising the safety of the subjects. In addition, the dosing in MAD period will be done under fed condition and PK on Day 1 in MAD under fed condition would allow preliminary assessment of CCI on exposure of PF-06826647.

CCI

PF-06826647 has demonstrated inhibition potential of MATE2K, and therefore, may have the potential to inhibit renal transport of creatinine. In order to provide an additional assessment of renal function during this trial, serum cystatin C will be collected in order to estimate glomerular filtration rate (GFR). Cystatin C is produced by all nucleated cells at a

constant rate and is 100% eliminated by glomerular filtration, without influence of renal transporters. The blood concentration of cystatin C is not substantially affected by diet, nutritional status or inflammatory disease. Therefore, serum cystatin C will serve as a nonbiased biomarker of GFR in addition to CCI [redacted]

[redacted] sites and subjects, unless prohibited by local regulations or ethics committee (EC) decision.

1.3.2. Preliminary Summary of Clinical Experience

As of March 25, 2018, the one, *on-going* clinical trial is the current study, C2501001. In this study, dosing of six single ascending dose cohorts and three multiple ascending dose cohorts has been completed, with 53 healthy adult subjects randomized and treated with PF-06826647 or placebo. To date, preliminary safety and PK data indicate that the stopping criteria , as outlined in Protocol Section 3.3, have not been met.

There have been no serious adverse events (including death) reported. Based on preliminary review of data, all reported adverse events (AEs) have been of mild intensity.

Preliminary pharmacokinetic data from the 3, 10, 30, 100, 400, and 1600 mg dose levels in SAD are summarized in Table 1. The results indicate that exposure (AUC and C_{max}) is lower than predicted by GastroPlus simulations presented in Table 3, therefore, the safety margin based on observed exposure is larger than what was initially expected. The increase in exposure appears to be less than proportional between 10 mg and 400 mg cohort and linear between 400 and 1600 mg. The preliminary PK data suggest longer terminal half-life at higher dose, possibly due to the biphasic concentration time profile and increased ability to measure the concentration for longer period at higher dose. The terminal half-life at 10 mg was approximately 6 hours whereas at 400 mg it was approximately 15 hours.

Table 1. Preliminary Summary of Draft Plasma PK Parameters of PF-06826647 Following Single Oral Dose Administration of PF-06826647 in Healthy Subjects (Fasted)

Single Dose (mg)	C_{max} (ng/mL)	AUC_{24} (ng.hr/mL)	AUC_{last} (ng.hr/mL)	$t_{½}$ hr
3	8 (38)	40 (56)	40 (56)	NR
10	47 (35)	346 (64)	355 (67)	6 (33)
30	78 (34)	543 (49)	639 (58)	NR
100	167 (55)	1160 (55)	1378 (53)	NR
400	329 (28)	1933 (28)	2135 (26)	15 (33)
1600	1218 (25)	9321 (34)	9796 (34)	13 (56)

Geometric mean (%CV) for all except arithmetic mean (%CV) for $t_{½}$, Abbreviations: %CV = percent coefficient of variation; NR = Not Reportable; AUC_{24}= Area under the concentration-time curve from time zero to 24 hours post single dose; C_{max} = Peak plasma concentration.

Preliminary pharmacokinetic data on Day 1 and Day 10 following multiple oral administration of PF-06826647 with standard meal at 30, 100 and 400 mg once daily (QD) are summarized in Table 2. By contrast with the PK parameters reported in Table 1, single dose administration with standard meal modestly increased the exposure of PF-06826647 by approximately 1.6 and 1.5 fold for AUC and C_{max}, respectively at 400 mg. The increase in exposure at steady state appears to be less than proportional with increase in dose. Multiple dosing over 10 days achieved steady state with modest accumulation (1.3 and 1.2 fold for AUC and C_{max} at 400 mg, respectively).

Table 2. Preliminary Summary of Draft Plasma PK Parameters of PF-06826647 Following Multiple Oral QD Dose Administration of PF-06826647 for 10 Days in Healthy Subjects (Fed-Standard Meal)

	Day 1		Day 10		
Dose (mg)	C_{max} (ng/mL)	AUC_{24} (ng.hr/mL)	C_{max} (ng/mL)	AUC_{24} (ng.hr/mL)	$t_{½}$ hr
30	84 (24)	664 (25)	85 (27)	752 (32)	9 (67)
100	267 (20)	1811 (23)	263 (30)	1950 (34)	7 (38)
400*	520 (30)	3488 (58)	689 (14)	4919 (32)	4(13)

Geometric mean (%CV) for all except arithmetic mean (%CV) for $t_{½}$; Abbreviations: %CV = percent coefficient of variation; NR = Not Reportable. AUC_{24}= Area under the concentration-time curve from time zero to 24 hours post single dose; C_{max} = Peak plasma concentration; *Partial data (only 4 subjects up to Day 11).

1.3.3. Dose Rationale

1.3.3.1. Dose Selection for FIH Study (Original Protocol Dose Rationale, 16 May 2017)

The data from in vitro pharmacologic and toxicologic studies on PF-06826647 and prior clinical experiences with other JAK inhibiting drugs were considered in dose selection for the first-in-human study.

The efficacious concentration (C_{eff}) for PF-06826647 was derived as a concentration that is expected to achieve approximately 80% average daily inhibition of IL-12. Based on the unbound IC_{50} value of IL-12 (Unbound IC_{50}=14 nM calculated based on total IC_{50}=53 nM, fraction unbound in human of 0.38 and RBC partition ratio of 1.4) determined by pSTAT

(phosphorylated signal transducer and activator of transcription proteins) modulation in in-vitro human whole blood and assuming Hill coefficient of 1, the calculated C_{eff} is 56 nM. The predicted $C_{av,24h}$ at a dose of 20 mg QD as SDD formulation is expected to produce approximately 80% daily average inhibition of IL12, therefore, 20 mg is a projected efficacious dose.

The human PK of PF-06826647 was predicted using GastroPlus physiologically based pharmacokinetic modeling by scaling in vitro hepatic clearances obtained from human liver microsomes (HLM) and human hepatocytes (HEP). HLM predicted a human clearance of 2.3 mL/min/kg, while that by HEP was 1.5 mL/min/kg. Given the confidence in CYP450s mediated metabolism as primary clearance mechanism and similarity between scaled clearances by HLM and HEP, 2 mL/min/kg was used for simulations of human PK concentrations. GastroPlus predicted dose dependent bioavailability with SDD formulation, which was used to improve the solubility and bioavailability of PF-06826647. At lower doses (~ <100 mg), the predicted bioavailability is expected to be >80% (see Table 3 below) but it is expected to decrease considerably at higher doses (~ >100 mg).

The nonclinical safety profile of PF-06826647 has been adequately characterized in rats and cynomolgus monkeys to support progression into human clinical studies up to 1 month in duration (Section 1.2.4 Non clinical safety studies). In cynomolgus monkeys, no observed adverse effect level (NOAEL) was established at 300 mg/kg/day while in rats, the NOAEL was established at 500 mg/kg/day and were the highest doses tested in both species. The resulting combined male and female mean NOAEL exposures in rats based on free drug were 16600 ng.hr/mL and 1870 ng/mL for the $AUC_{24,ss}$ and C_{max}, respectively. The corresponding values for the monkey were 19900 ng.h/mL and 1790 ng/mLfor AUC and C_{max}, respectively. No clear differences in the species sensitivity were noted. Since rat had lower free $AUC_{24,ss}$, exposure limits were based on the NOAEL exposures observed in rats ($AUC_{24,ss}$ = 16600 ng.hr/mL and C_{max} =1870 ng/mL).

Human PK parameter estimates for PF-06826647 along with toxicokinetic data and predicted pharmacological effect based on in vitro inhibition of cytokines (IL12, IL23 and IFN-α) were used to estimate the starting dose in this study. Based on the predicted average concentrations over dosing interval ($C_{av,24\ h}$) and in vitro IC_{50} in whole human blood (after accounting for fraction unbound of 0.38 and RBC partitioning of 1.4), the projected percent inhibitions of cytokines IL-12, IL-23 and IFN-α (IL-12:Total IC_{50}=53 nM,Unbound IC_{50}=14 nM; IL-23:Total IC_{50}=112 nM,Unbound IC_{50}=30 nM; IFNα:Total IC_{50}=66 nM,Unbound IC_{50}=18 nM; Unbound IC_{50} calculated based on fraction unbound in human 0.38 and RBC partition ratio=1.4) at the proposed starting single dose of 3 mg are approximately 43, 27 and 38%, respectively. In the FIH study with TYK2/JAK1 inhibitor (PF-06700841) as a single dose of 200 mg, these cytokines were inhibited up to >95% without any safety concern. The planned starting single dose of 3 mg is predicted to provide, relative to the exposures (based on free concentrations) on Day 29 observed from the highest dose (500 mg/kg/day) administered to rats, exposure margins of 260-fold for C_{max} and 185-fold for AUC_{24}. The maximum recommended starting dose based on human equivalent dose (HED) approach with safety factor of 10 is 225 mg. The proposed starting dose of 3 mg is approximately 1/1880th of the HED based on the highest dose

(500 mg/kg/day) administered to rats. The expected levels of inhibition of these cytokines will provide minimal pharmacological activity and no safety concerns at the starting dose of 3 mg.

The proposed single ascending (SAD) doses for this study are 3, 10, 30, 100, 200 and 400 mg to identify the expected clinically efficacious dose range in humans and to provide safety coverage for the expected clinically-relevant dose range. The margins for the highest proposed single dose (400 mg) established on the free exposures in rat are projected to be approximately 4- fold for C_{max} and 3- fold for AUC_{24} which are well within the NOAEL exposure.

The resulting mean total and free exposures and associated margins following the proposed single doses of PF-06826647 during the single ascending dose period are provided in Table 3.

Table 3. Predicted Mean Human Total and Free Exposures and Associated Margins Following Single Dose Administration of PF-06826647

Dose[a] (mg)	Predicted Bioavailability[b] (%)	Predicted Human Exposure of plasma PF-06826647[b]				Predicted Safety Margin based on *free* plasma PF-06826647[d]	
		Free C_{max} (ng/mL)	Total C_{max}[c] (ng/mL)	*Free* AUC_{0-24} (ng•h/mL)	Total AUC_{0-24}[c] (ng•h/mL)	C_{max}[e]	AUC_{0-24}[f]
3	88	7	19	90	237	260	185
10	87	23	61	296	778	80	56
30	84	66	174	846	2226	28	20
100	69	186	489	2287	6017	10	7
200	56	304	800	3686	9701	6	5
400	41	444	1168	5409	14233	4	3

AUC_{0-24} = Area under the concentration time curve from time zero to 24 hours after single dose; CL = Clearance; C_{max} = Peak plasma concentration; NOAEL = No observed adverse effects level.

a. Depending on the available safety and PK data, dose escalation may be adjusted to doses other than those outlined above with intermediate doses evaluated instead of or in addition to the planned dose levels while following dose escalation and stopping rules outlined in Section 3.2.
b. GastroPlus predicted. Exposure prediction was based on scaled clearance (CL = ~2 mL/min/kg) from human liver microsome and human hepatocytes.
c. Calculated using unbound values correcting for protein binding in humans (Human unbound fraction=0.38).
d. Derived using Day 29 exposure of PF-6826647 at NOAEL (500 mg/kg/day) from 1 month rat toxicity study. Exposure on Day 29 in rats at 500 mg/kg/day (NOAEL): Total AUC_{24}=92,100 ng.h/mL, free AUC_{24}=16,600 ng.h/mL, Total C_{max}=10,400 ng/mL, free C_{max} = 1870 ng/mL; rat unbound fraction = 0.18.
e. C_{max} Margins=C_{max} in Rat on Day 29/Predicted C_{max} in human post single dose.
f. AUC margins = AUC_{24} in Rat on Day 29/Predicted AUC_{0-24} in human post single dose.

The multiple dose period is planned to be initiated at the 10 mg QD dose level; however, the starting dose in MAD may be adjusted based on available PK, CC and safety data from the SAD cohorts. Based on the predicted steady state exposures ($C_{max,ss}$ and $AUC_{24,ss}$), 10 mg QD is expected to provide margins of 71-fold for $C_{max,ss}$ and 50-fold for $AUC_{24,ss}$ relative to the free exposure in rat on Day 29. The proposed doses for the multiple ascending dose (MAD) period are 10, 30, 100 and 200 mg QD x10 days. All dose levels listed are

nominal since doses will be driven by exposure. The highest proposed dose of 200 mg QD is predicted to have margins of 5-fold and 4-fold for $C_{max,ss}$ and $AUC_{24,ss}$, respectively.

Listed in Table 4 are the mean exposure (total and free) and associated margins following the proposed QD dosing regimen for 10 days.

Table 4. Predicted Mean Human Total and Free Exposures and Associated Margins Following Once Daily Dosing of PF-06826647 for 10 Days

Dose[a] (mg) QD	Predicted Bioavailability[b] (%)	Predicted Human Exposure of plasma PF-06826647[b]				Predicted Safety Margin based on *free* plasma PF-06826647[d]	
		Free C_{max} (ng/mL)	Total C_{max}[c] (ng/mL)	*Free* $AUC_{24,ss}$ (ng.h/mL)	Total $AUC_{24,ss}$[c] (ng.h/mL)	C_{max}[e]	AUC_{0-24}[f]
10	87	26	69	332	874	71	50
30	84	76	199	962	2531	25	17
100	69	217	570	2664	7010	9	6
200	56	348	916	4249	11182	5	4

$AUC_{24,ss}$= Area under the concentration-time curve from zero to 24 hours post dose at steady state; CL = Clearance; C_{max} = Peak plasma concentration; C_{max},ss = Maximum concentration at steady state ; QD = Once daily

a. Depending on the available safety and PK data, dose escalation may be adjusted to doses other than those outlined above with intermediate doses evaluated instead of or in addition to the planned dose levels while following dose escalation and stopping rules outlined in Section 3.2.
b. GastroPlus predicted. Exposure prediction was based on scaled clearance (CL =~ 2 mL/min/kg) from human liver microsome and human hepatocytes.
c. Calculated using unbound values correcting for protein binding in humans (Human unbound fraction=0.38).
d. Derived using Day 29 exposure of PF-6826647 at NOAEL (500 mg/kg/day) from 1 month rat toxicity study. Exposure on Day 29 in rats at 500 mg/kg/day (NOAEL): Total AUC_{24}=92,100 ng.h/mL, free AUC_{24}=16,600 ng.h/mL, Total C_{max}=10,400 ng/mL, free C_{max} = 1870 ng/mL; rat unbound fraction = 0.18.
e. C_{max} Margins=C_{max} in Rat on Day 29/Predicted C_{max} in human post single dose.
f. AUC margins = AUC_{24} in Rat on Day 29/Predicted AUC_{0-24} in human post single dose.

All the doses in SAD or MAD cohorts except starting dose of 3 mg in SAD cohort are nominal and may be adjusted, as the study progresses depending upon emerging PK, [redacted] safety, and tolerability data. Other intermediate doses or lower doses may be administered instead of the planned doses, or changes in dosing frequency or titration schemes may be proposed for MAD cohorts if safety/tolerability issues become apparent, if evidence of nonlinear PK dictates the need to escalate more slowly, or if subsequent doses are predicted to result in exposures that exceed the target limits. However, the projected exposure for the modified doses or additional cohorts will be equal to or less than a free AUC of 16600 ng.h/mL or free C_{max} of 1870 ng/mL following either single dose or multiple dose administration to ensure that the projected exposure of the altered planned dose scheme does not exceed the exposure limit.

1.3.4. Updated Dose Rationale Based on Emerging Clinical Data (Protocol Amendment 2, 20 December 2017)

Based on the evaluation of the emerging human PK data, the observed exposure was lower than predicted and the increase in exposure appears to be less than dose proportional except at 3 mg SAD (dosed as suspension). Protocol amendment 1 updates the initially proposed dose levels with the aim to achieve exposure that will allow a full exploration of the clinical efficacy in future clinical studies. Also, the MAD cohort will be dosed under fed condition in a hope to improve the bioavailability of PF-06826647 [redacted]

Under protocol amendment 1, the proposed dose of SAD Cohort 5 will be 400 mg. Accounting for the less than dose proportional increase in AUC_{24} and C_{max} observed at 100 mg, 400 mg is predicted to provide approximately ~2 fold higher exposure than 100 mg. The doses of Cohort 6 and two optional SAD cohorts (Cohort 7 and Cohort 8) will be based on the emerging PK, [redacted] and Safety data but in all cases will be selected to provide a projected exposure of no more than approximatelly 3 fold the previous highest dose cohort exposure and less or equal to the PK stopping limit. All dose levels listed in Table 5 are nominal and any of the listed or intermediate doses may be used based on emerging PK, [redacted] and safety data. However, the maximum dose tested will not exceed 1600 mg (16 × 100 mg Tablets), based on practical limitations. The projected safety margin for AUC_{24} and C_{max} at 1600 mg SAD is approximately 8 and 7 fold, respectively (Table 5).

The projected PK parameters in Table 5 are based on preliminary exploratory population PK model from draft human PK data up to SAD Cohort 4, assuming nonlinear decrease in bioavailability with increase in dose. The projected geometric mean total and free exposures and the associated projected margins for doses (up to 1600 mg) are provided in Table 5.

CCI [redacted]

[redacted]

CCI [redacted]

1.3.4.1. Dose Selection for Psoriasis Patients

Two cohorts of subjects with moderate to severe plaque psoriasis are proposed to be studied at two dose levels to be administered PF-06826647/placebo QD for 28 days. The initial psoriasis cohort will commence at 400 mg PF-06826647 (or placebo). The nominal dose for second psoriasis cohort dose level is planned to be 100 mg PF-06826647 (or placebo), which may be adjusted based on results from the 400 mg psoriasis cohort. These dose levels are selected based on preliminary PK, CCI safety and tolerability data up to 1600 mg single dose in SAD Period and up to 400 mg QD for 10 days in MAD Period in healthy subjects.

Dose selection for this part of the study is based on the observed PF-06826647 exposure in healthy subjects and in vitro potency data aiming to achieve high inhibition of TYK2 dependent cytokines while maintaining selectivity over other JAK enzymes and modulation of associated genes. The $C_{av,24}$ at steady state at 100 and 400 mg dose in healthy subjects was approximately 81 and 205 ng/mL, respectively. Based on the IC_{50} value of IL-12 (total IC_{50}=53 nM) determined by pSTAT modulation in in vitro human whole blood, RBC partition ratio of 1.4 and assuming Hill coefficient of 1, the average daily inhibition of IL-12 at 100 and 400 mg will be approximately 85 and 93%, respectively. Similarly, IFNα (total IC_{50} = 66 nM) will have average daily inhibition of approximately 82 and 92% while the average inhibition of IL-23 (total IC_{50} = 112 nM) will be approximately 73 and 87% at

100 and 400 mg, respectively. These two doses are also supported by preliminary evidence of TYK2 pharmacology modulation of Type-I IFN genes.

In addition, based on data observed to date in healthy subjects (see Section 1.3.2) these doses are expected to be safe and well tolerated. Although, based on in vitro data, the average inhibition of EPO (total IC_{50} = 547 nM) is expected to be approximately 35% and 58% at 100 and 400 mg respectively, no clinically significant changes in hemoglobin were observed in healthy subjects at the same dose. Based on the observed steady state free exposures ($C_{max,ss}$ and $AUC_{24,ss}$), 400 mg QD is expected to provide margins of about 7-fold for $C_{max,ss}$ and about 9-fold for $AUC_{24,ss}$ relative to the free exposure in rat on Day 29 (NOAEL).

The initial psoriasis cohort will commence at 400 mg QD PF-06826647 for 28 days. Dosing of the second psoriasis cohort will occur after completion of 400 mg psoriasis Cohort 28 day dosing, while the follow up periods of the two cohorts may be parallel or staggered based on operational considerations. Following interim analysis review of efficacy data from 21 subjects (14 active and 7 placebo) completing through study Day 28 in the 400 mg psoriasis cohort, the PF-06826647 dose level for the next psoriasis cohort may be adjusted within the range of safe and well tolerated doses established in healthy subjects.

The tablets administered in psoriasis subjects will be the same as the tablet administered to healthy subjects. The subjects will be required to take the tablets in the morning with standard meal in order to achieve higher exposure.

2. STUDY OBJECTIVES AND ENDPOINTS

Objectives and Endpoints: Healthy Subject Single and Multiple Ascending Dose Cohorts	
Primary Objective(s):	**Primary Endpoint(s) - Safety:**
• To determine the safety and tolerability of escalating single and multiple doses of PF-06826647 administered to healthy subjects.	• Vital signs (blood pressure, pulse rate, oral temperature). • Physical examination findings over time. • 12-lead ECG parameters. • Incidence and severity of treatment emergent adverse events and withdrawals due to treatment emergent adverse events. • Incidence and magnitude of treatment emergent clinical laboratory abnormalities including hematology (with differentials), fibrinogen, chemistry, fasting glucose, lipids, urinalysis. • Change in 24 hour creatinine clearance from Day -1 and Day 10 (MAD only).
Secondary Objective(s):	**Secondary Endpoint(s):**
• To characterize the PK of PF-06826647 in plasma and urine (urine PK in multiple ascending dose period only) following oral administration of	• Systemic pharmacokinetics parameters (defined in Section 9.3.1) will include:

escalating single and multiple oral doses to healthy subjects.	• Single Dose: C_{max}, T_{max}, AUC_{inf}, AUC_{last}, AUC_{24}, C_{max}(dn), AUC_{inf}(dn), $AUC_{last(dn)}$, $t_{½}$, MRT, V_z/F, and CL/F (if data permit). • Multiple Dose: • Day 1: C_{max}, T_{max}, AUC_{tau} (tau=12 or 24 hours), C_{max}(dn), AUC_{tau}(dn). • Day 10: C_{max}, T_{max}, AUC_{tau} (tau=12 or 24 hours), C_{max}(dn), AUC_{tau}(dn), t½, C_{min}, C_{av}, R_{ac}, $R_{ac,Cmax}$, PTR, MRT, V_z/F,CL/F (if data permit). • Urinary Pharmacokinetics (defined in Section 9.3.1;for healthy subjects, multiple ascending dose period only): Ae_{tau} and Ae_{tau}%, CLr (if data permit).
CCI [redacted]	[redacted]
[redacted]	[redacted]

[redacted]	CCI [redacted]

Objectives and Endpoints: Psoriasis Multiple Dose Cohorts	
Primary Objectives - Safety	**Primary Endpoints - Safety**
• To determine the safety and tolerability of multiple dose administration of PF-06826647 in psoriasis subjects.	• Vital signs (blood pressure, pulse rate, and oral temperature). • Physical examinations fndings over time. • 12-lead ECG parameters. • Incidence and severity of treatment emergent adverse events and withdrawals due to treatment emergent adverse events. • Incidence and magnitude of treatment emergent clinical laboratory abnormalities including hematology (with differentials) chemistry, fasting glucose, lipids, urinalysis.
Secondary Objectives	**Secondary Endpoints**
• To characterize the PK of PF-06826647 in plasma following oral administration of multiple oral doses to plaque psoriasis subjects. • To evaluate the efficacy of PF-06826647 in moderate to severe plaque psoriasis.	• Multiple Dose (defined in Section 9.3.1): C_{max}, T_{max}, AUC_{tau}, $C_{max}(dn)$, $AUC_{tau}(dn)$, $t_{½}$, PTR, C_{min}, C_{av}, MRT, V_z/F and CL/F (if data permit). • Change from baseline in psoriasis area and severity index (PASI) score at Day 28.
CCI [redacted]	[redacted]
[redacted]	[redacted]

3. STUDY DESIGN

3.1. Study Overview

The study may be conducted at 1-3 study sites in the United States.

This study is a Phase 1 combination, within cohort, randomized, double blind, third-party open, placebo-controlled, parallel group study with single- and multiple-dose escalation in healthy adult subjects, and multiple dosing in subjects with plaque psoriasis.

Subjects will be screened within 28 days prior to administration of study drug to confirm that they meet the subject selection criteria for the study. A summary of the schedule of study participation and procedures for the single- and multiple ascending dose periods of the study are provided in their respective Schedule of Activities.

3.1.1. Healthy Subject Single and Multiple Ascending Dose Periods

In the combined single ascending and multiple ascending dose (SAD/MAD) healthy subject cohorts there will be approximately 8 subjects per dose level; 6 subjects will receive PF-06826647 and 2 subjects will receive placebo per the randomization code.

Healthy subjects will be randomized (once) into the SAD period, at which time, they will receive treatment assignment (active PF-06826647 dose level or placebo) for both the SAD and MAD periods. Subjects will receive the same blinded treatment assignment (ie, the same dose level of active PF-06826647 or placebo) throughout in both the SAD (Period 1) and MAD (Period 2) periods.

During the single ascending dose (SAD) period, healthy subjects in Cohort 1 to Cohort 6 will receive single doses of 3, 10, 30, 100, 400, or 1600 mg of PF-06826647 or placebo in a dose escalation format as shown in the Study Schema (Figure 1). The doses and meal condition of optional cohorts (Cohort 7 and Cohort 8) will be decided on emerging PK, CCI and safety data from prior SAD and MAD cohorts. Dose escalation to subsequent cohorts will be based on a minimum of 3 days of safety data and PK over 24 hours in a minimum of 6 subjects enrolled in a cohort. Subjects will reside in the clinical research unit (CRU) for the single ascending dose phase from Day -1 until completion of protocol assessments on Day 4. Dosing occurs on Day 1. Subjects will return to the unit on Day 8 (±1) day for the end of single dose period assessment and PK sample.

At least 14 days (minimum wash-out period) will separate the beginning of the single and multiple dose periods (ie, at least 14 days will separate the single dose administered in the SAD and the first QD dose in the MAD); however, the minimum wash-out period may be adjusted based on emerging PK data. Based on the PK predictions and emerging PK data from this study, the currently planned starting dose in the MAD period is 30 mg (previously, a PF-06826647 starting dose of 10 mg was planned for the MAD period under the original protocol) is not expected to provide pharmacologically relevant exposure. In the multiple ascending dose (MAD) period, healthy subjects in Cohort 3 to Cohort 6 in Period 2 will receive doses of 30, 100, 400, or 1200 mg QD of PF-06826647 or placebo for 10 days (Day 1 through Day 10) with standard meal. The dose of Cohort 6 in MAD (Period 2) may be adjusted based on emerging data from earlier MAD cohorts in the trial. Subjects will be housed for the duration of the multiple dosing period, discharged on the morning of Day 14. Subjects will return for outpatient visits on morning of Day 17 for PK sample collection and Day 28 (±3 days) for end of study procedures. Based on emerging PK data, subject may be asked to return between Day 17 and Day 28 for an additional outpatient visit for PK sample

collection. The additional PK sample will allow characterization of terminal half-lives at higher dose cohorts.

The multiple ascending dose study is planned to be initiated in the same subjects who previously participated in the single dose period at the same dose level, when possible (except for the optional twice daily, BID cohort and optional Japanese cohort). The highest dose to be tested in MAD will not exceed the highest dose tested in SAD cohort. Except the highest dose cohort, dosing in the MAD period will commence at the intended dose level (eg, 30 mg QD) if adequate single dose safety is demonstrated for next dose level (eg, 100 mg SAD). Subsequent MAD cohorts at higher dose levels (eg, 100 mg QD) will not be initiated until the single dose safety/tolerability has been established up to next dose level (eg, 400 mg), and a minimum of 10 days of safety and PK data from the preceeding multiple dose cohort (eg, 10 mg QD) from at least 6 subjects (with at least one subject on placebo) has been reviewed. The remainder of the cohorts (except highest dose cohort) will follow a similar escalation paradigm. Dosing in highest dose MAD cohort will commence if adequate safety is demonstrated in SAD cohort at the same or higher dose level and the projected exposure at steady state does not exceed NOAEL.

Twice daily (BID) dosing (for 10 days) may be evaluated as a separate cohort based on emerging PK data from this FIH study. Dosing in the BID cohort will not commence until review of safety data from the equivalent QD MAD cohort (minimum review of 10 day safety and PK data in at least 6 subjects, with at least one subject on placebo).

An optional Japanese cohort may also be included. If conducted, the dose administered will be equal to or less than the maximum PF-06826647 dose level administered in the healthy volunteer MAD period. Up to 8 subjects (including subjects on placebo) may be included in the optional Japanese cohort.

Administration of investigational product will be in fasted state in the SAD period and under standard meal conditions in MAD and in psoriasis cohorts. Based on the emerging PK, CCI [redacted] and safety data, the meal condition requirement in SAD, MAD and psoriasis cohorts may be changed.

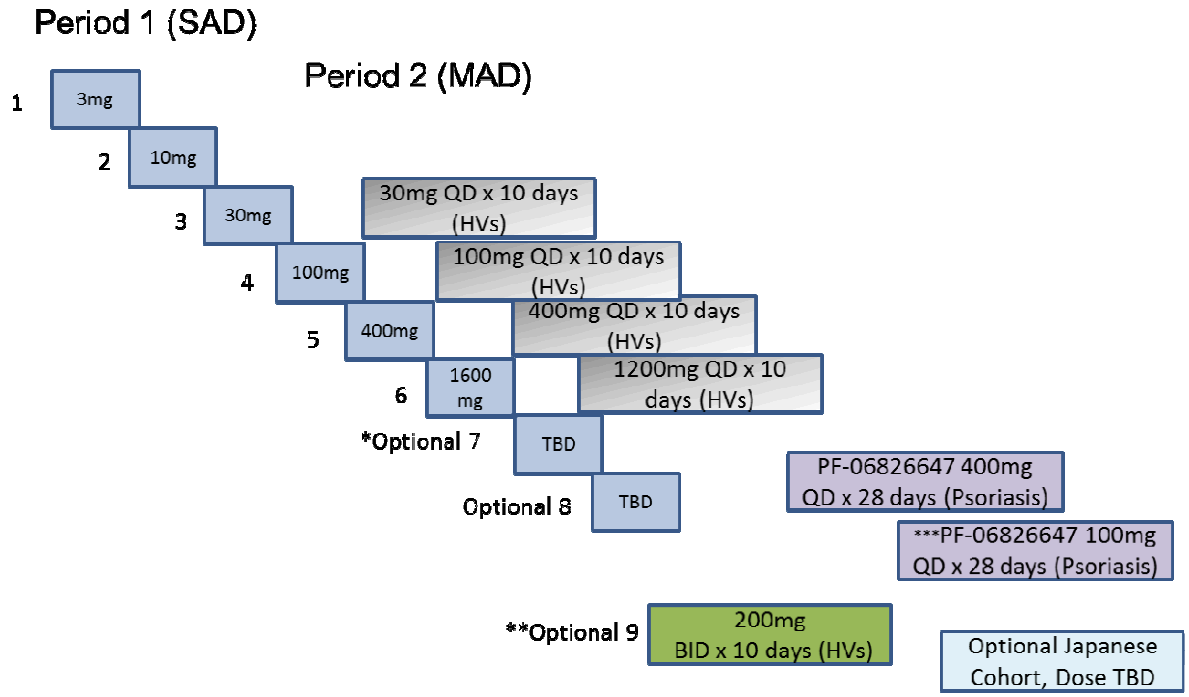
During the single and multiple ascending dose periods the dose increments and planned doses may be adjusted, as the study progresses dependent upon emerging PK, safety, and tolerability data. Other intermediate doses or lower doses may be administered instead of the planned doses, or changes in dosing frequency or titration schemes may be proposed for MAD cohorts if safety/tolerability issues become apparent, if evidence of nonlinear PK dictates the need to escalate more slowly, or if subsequent doses are predicted to result in exposures that exceed the target limits. Any potential altered dose scheme will be equal to or less than a projected 3-fold increase in exposure from the previous highest dose if a higher dose is warranted to achieve exposure. The projected exposure will be equal to or less than a free AUC of 16600 ng.h/mL or free C_{max} of 1870 ng/mL following either single dose or multiple dose administration to ensure that the projected exposure of the altered planned dose scheme does not exceed the exposure limit.

3.1.2. Psoriasis Multiple Dose Cohorts

In the multiple dose psoriasis subject cohorts, approximately 42 subjects will be enrolled with approximately 14 subjects receiving placebo, and approximately 28 subjects receiving one of two possible PF-06826647 dose levels, for 28 days. PF-06826647 dose range for the psoriasis cohorts will be selected based on emerging PK, [redacted] and safety data from the healthy subjects SAD/MAD periods. Refer to Protocol Section 1.3.4.1 for psoriasis dose selection rationale. QD dosing is planned for psoriasis subjects, however, daily dosing regimen (eg, QD, BID) may be adjusted based on emerging PK data from the SAD/MAD periods. Psoriasis subjects who discontinue early from the trial may be replaced at the discretion of the sponsor. PF-06826647 dose level in psoriasis may be adjusted based on emerging clinical data from the planned interim analysis, at the discretion of the Sponsor. Any potential PF-06826647 dose adjustments for psoriasis Cohort 2 will be applied after review of PK, [redacted] and safety data up to 28 day in the 400 mg psoriasis cohort.

Initiation of dosing in psoriasis subjects will be based on available safety data from the healthy subject MAD period. Psoriasis subjects enrolled into the multiple dosing period will receive PF-06826647 or placebo (QD) for 28 days, with a 56 day follow-up period post last dose. Doses will be selected based on emerging PK, PD and safety data from the study (not to exceed C_{max} and AUC_{0-24} limits of 1870 ng/mL and 16,600 ng·h/mL, respectively). Dosing in psoriasis subjects will commence if adequate safety is demonstrated in healthy subjects participating in the MAD period at the equivalent dose level. At a minimum, 10 day safety and PK data from at least 6 healthy subjects (with at least one subject on placebo) receiving the equivalent QD dose level will be reviewed to confirm that a given PF-06826647 dose is safe and well tolerated before administering PF-06826647 to psoriasis subjects. Subjects will be housed through Day 28 of the multiple dosing period, discharged on Day 28, to return for outpatient visits on the mornings of Days 35 (±3 days), 42 (±3 days), 56 (±3 days) and 84 (±3 days)(end of study). The 28 day treatment duration is supported by preclinical toxicology data and will facilitate assessment of [redacted], as well as assessment of clinical endpoints (eg, PASI).

Figure 1. Study Schema



Numbers 1 – 8 refer to subject cohorts. Subjects completing the SAD period will continue into the MAD period when applicable, after protocol defined washout and follow up.

* Cohorts 7 and 8 are optional single dose cohorts that may be conducted at discretion of Sponsor and based on emerging PK data. If conducted, the dose and meal condition will be decided based on emerging PK, PD, and safety data from the multiple ascending dose period of the trial.

** Cohort 9 is an optional cohort for assessment of twice daily (BID) PF-06826647 dosing. BID dose level will be determined based on emerging PK, PD, safety and tolerability data. The planned PF-06826647 dose level to be administered in the BID cohort is 200 mg twice daily (total daily dose of 400 mg).

*** Based on interim analysis results from 400 mg psoriasis cohort, the PF-06826647 dose level for psoriasis Cohort 2 may be adjusted. The maximum dose administered to psoriasis subjects will not be expected to exceed the exposure at the maximum tolerated dose in the healthy subject MAD period.

HVs = healthy volunteers

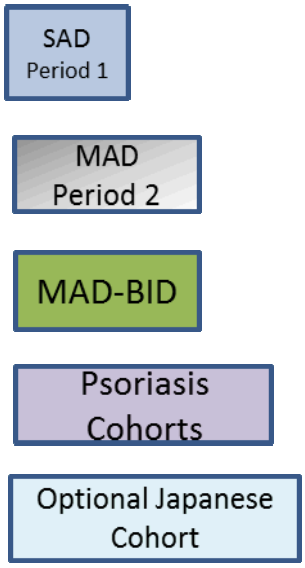
All cohorts are placebo controlled .

Note on optional Japanese subject cohort: if conducted, administration of PF-06826647 (or matching placebo) to Japanese subjects will occur once daily for 10 day duration, and subjects will follow the MAD period schedule of activities.

Figure 2. Legend for Figure 1

SAD = Single ascending dose Period 1 QD = once daily

MAD=multiple ascending dose Period 2 BID=twice daily



3.2. Dose Escalation and Stopping Rules

The following dose escalation rules apply to the single and multiple ascending dose healthy subject cohorts. Individual stopping rules for healthy subjects (SAD/MAD) and psoriasis subjects are also outlined below.

Dose-escalation stopping rules will be used to determine whether the maximal tolerated dose has been attained. Dose escalation may be stopped if it is determined that the limits of safety and/or tolerability have been reached. This decision will be made after a discussion takes place between the sponsor study team and the investigator. The sponsor study team may not overrule the investigator's decision to stop dose escalation. If dose escalation is stopped because of any of these criteria, additional cohorts may receive the same or lower doses of the investigational product.

The dose escalation will be terminated based on the following criteria:

- If 50% or more of the subjects receiving active drug at a given dose level (but not subjects receiving placebo) develop similar clinically significant laboratory, electrocardiogram (ECG), or vital sign abnormalities as described below in Section 3.3), or severe adverse events (AEs) in the same organ class, indicating dose-limiting intolerance.

- Dosing will be paused for any serious adverse event (SAE) that occurs in a subject receiving active treatment until causality is fully assessed by the principal investigator (PI) and sponsor. Dosing may resume if the SAE is determined to be not drug-related

by the PI and sponsor. If the SAE is determined to be either drug-related or unknown, either dosing will cease or the SAE will be evaluated by the sponsor's protocol review committee (or similar review group), which is independent of the study team and investigators. If the protocol review committee determines that dosing may resume, a plan that mitigates risks to subjects with the resumption of dosing will be implemented. Such a plan could include a revision of inclusion/exclusion criteria, repeating or reducing the dose, or adding appropriate safety monitoring.

- It is determined that the limit of safety and/or tolerability has been reached. This decision will be made following discussions between the study team and the investigator.

- Other findings that, at the discretion of the study team and investigator, indicate that dose escalation should be halted.

- If, at any dose level, the average exposure reaches or exceeds the pharmacokinetic (PK) stopping limits based on free C_{max} and AUC_{0-24} values of 1870 ng/mL and 16,600 ng.h/mL, respectively.

- If, based on the observed data, the group mean maximum observed concentration (C_{max}) or area under the curve (AUC) (based on total plasma concentration) of the next planned dose is projected to exceed the escalation limits, that dose will not be explored. Modified doses may be explored if they are not expected to exceed PK stopping criteria.

Progression to the next single dose level will occur if the last dose was well tolerated and after satisfactory review of the available safety and PK data. Minimum data required for dose escalation review includes 24 hour PK data, adverse event/serious adverse events, vital sign and ECG data, urinalysis, chemistry and hematology laboratory results through Day 3 in at least 6 subjects (with at least one subject on placebo)within a given dose cohort.

Initiation of the multiple ascending dose study will commence at the 10 mg dose level if adequate safety is demonstrated for single doses up to 30 mg. Similarly, the 30 mg dose level will not be initiated until the safety/tolerability has been established up to100 mg single dose and a minimum of 10 days of safety data (vital sign and ECG data, urinalysis, chemistry, hematology, adverse event data) and 10 day PK data from the preceding multiple dose cohort from at least 6 subjects (with at least one subject on placebo). The remainder of the cohorts will follow a similar escalation paradigm (except for the highest MAD cohort dose level, which will be equal to or less than the maximum SAD dose level tested). Dosing in highest dose MAD cohort will commence if adequate safety is demonstrated in SAD cohort at the same or higher dose level and the projected exposure at steady state does not exceed NOAEL. Dose levels may be adjusted based on emerging PK data from this study, however, this escalation paradigm will still apply.

3.3. Individual Stopping Rules for the Healthy Subjects during the Single and Multiple Ascending Dose Periods

Adverse Events:

- Dosing will be discontinued for any treatment emergent serious adverse event (SAE) that occurs in a subject receiving active treatment unless the SAE is clearly unrelated to study drug (eg, subject is the victim of a motor vehicle accident).

- Serious infections, defined as any infection (viral, bacterial, and fungal) requiring parenteral antimicrobial therapy or hospitalization.

Laboratory, Vital Sign, and ECG Abnormalities:

Individual stopping rules will be based on repeated measures (single repeat preferably performed within 24 hours of initial result) of the parameters outlined below.

- Grade 3 lymphopenia (<500 cells/mm^3).

- Grade 3 neutropenia (<1000 cells/mm^3).

- Grade 3 ALT/AST (>5x upper limit of normal (ULN) when not accompanied by an increase in bilirubin).

- Grade 3 bilirubin (>2.0 x ULN when not accompanied by an increase in ALT/AST).

- Changes in liver function tests that meet Hy's Law criteria.

- Serum creatinine ≥1.5 x ULN.

  Note: An increase of ≥0.3 mg/dL (or ≥26.5 µmol/L) in serum creatinine relative to subjects' own baseline measurement should trigger another assessment of SCr within 24-hours from awareness. See Potential Cases of Acute Kidney Injury for further guidance.

- Grade 2 Hemoglobin <10 g/dL.

- Grade 2 Platelets <75,000/mm^3 or >750,000/mm^3.

- 12-lead ECG demonstrating QTc ≥500; or a QRS interval ≥140 msec or ≥50% increase from baseline; PR interval ≥300 msec or 25% increase over baseline when baseline >200 msec.

Blood pressure or pulse rate measurements meeting criteria for individual stopping rules should be repeated at least twice, separated by at least 5 minutes, with the subject at rest, supine. If confirmed to be abnormal and confirmed to be clinically significant by investigator, dosing should be stopped and the blood pressure/pulse should be followed

periodically, as deemed appropriate by the investigator, until the blood pressure/pulse rate are returned to within normal limits or deemed acceptable by the investigator.

- Vital sign abnormalities:
  - Systolic blood pressure <90 mmHg or >160 mm Hg;
  - Diastolic blood pressure <50 mmHg or >100 mm Hg;
  - Pulse rate supine/sitting <36 or >120 beats per minute (bpm); standing <36 or >140 bpm.

Other:

- Subjects non-compliant with study treatment.

3.4. Individual Stopping Rules for Psoriasis Subjects

Treatment with PF-06826647 will be discontinued and the subject withdrawn from this study for:

Adverse Events:

- Serious infections, defined as any infection (viral, bacterial, and fungal) requiring parenteral antimicrobial therapy or hospitalization.
- Other treatment emergent serious or severe AEs, after consultation with the Pfizer clinician.

Laboratory, Vital Sign, and ECG Abnormalities:

Individual stopping rules below will be based on repeated measures (single repeat preferably performed within 24 hours of initial result) of the parameters outlined below.

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; <75.0x0x10^9/L
WBC	<3000/mm^3; <3.0x10^9/L
Lymphocytes	<800/mm^3; <0.8x10^9/L
Chemistry	
AST	>2.5x ULN
ALT	>2.5x ULN
Creatinine (serum)	>1.5x ULN
Total bilirubin [a]	>1.5x ULN

[a] Total bilirubin ≥1.5 x ULN; subjects 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.

- Changes in liver function tests that meet Hy's Law criteria.

Note: An increase of ≥0.3 mg/dL (or ≥26.5 μmol/L) in serum creatinine relative to subjects' own baseline measurement should trigger another assessment of SCr within 24-hours from awareness. See Potential Cases of Acute Kidney Injury for further guidance.

- 12-lead ECG demonstrating QTc ≥500; or a QRS interval ≥140 msec or ≥50% increase from baseline; PR interval ≥300 msec or 25% increase over baseline when baseline >200 msec.

Blood pressure measurements meeting criteria for individual stopping rules should be repeated at least twice, separated by at least 5 minutes, with the subject at rest, supine. If confirmed to be abnormal, and confirmed to be clinically significant by investigator, dosing should be stopped and the blood pressure should be followed periodically, as deemed appropriate by the investigator, until the blood pressure are returned to within normal limits or deemed acceptable by the investigator.

- Diastolic: recurrent or persistent (≥24 hrs) or symptomatic increase from baseline, in same posture, by >20 mmHg.

- Systolic: recurrent or persistent (≥24 hrs) or symptomatic increase from baseline, in same posture, by >30 mm Hg.

Other:

- Subjects non-compliant with study treatment.

3.5. Discontinuation/End of Treatment Monitoring for Adverse Events, Laboratory, Vital Signs and ECG Abnormalities

Any subject meeting discontinuation criteria will be followed up every 1 to 2 weeks, with retesting as appropriate, until the event has returned to normal or baseline levels or is deemed clinically stable.

Additional follow-up visits may occur as needed until any clinically relevant abnormalities or adverse events have resolved, returned to a baseline state, or are deemed clinically stable.

4. SUBJECT ELIGIBILITY CRITERIA

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

4.1. Inclusion Criteria: Healthy Subject Single/Multiple Ascending Dose Cohorts

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Healthy female subjects of non-childbearing potential and/or male subjectsbetween the ages of 18 and 55 years, inclusive (Healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure and pulse rate measurement, 12-lead ECG and clinical laboratory tests).

2. Female subjects of non-childbearing potential must meet at least 1 of the following criteria:

    a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state.

    b. Have undergone a documented hysterectomy and/or bilateral oophorectomy.

    c. Have medically confirmed ovarian failure.

    All other female subjects (including females with tubal ligations) areconsidered to be of childbearing potential.

3. Body Mass Index (BMI) of 17.5 to 30.5 kg/m^2; and a total body weight >50 kg (110 lbs).

4. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.

5. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

6. No evidence of active or latent or inadequately treated infection with Mycobacterium tuberculosis (TB) as defined by the following:

    a. negative Interferon Gamma Release Assay (IGRA) (with the following acceptable assays: QuantiFERON^{R}-TB Gold (QFT-G) test, T-SPOT TB, QuantiFERON-TB Gold In-Tube test (QFT-GIT)) performed during Screening or within 3 months prior to Day 1.

    AND

    b. No history of either untreated or treated latent or active TB infection.

A subject who is currently being treated for either latent or active TB infection is to be excluded.

7. Additional criterion for subjects to be enrolled in Japanese cohort only: Japanese subjects who have four Japanese biologic grandparents born in Japan.

4.2. Exclusion Criteria: Healthy Subject Single/Multiple Ascending Dose Cohorts

Subjects presenting with any of the following characteristics/conditions will not be included in the study:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at time of dosing).

2. Any condition possibly affecting drug absorption (eg, gastrectomy).

3. A positive urine drug screen.

4. History of regular alcohol consumption exceeding 7 drinks/week for females or 14 drinks/week for males (1 drink = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor) within 6 months of screening.

5. Treatment 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, whichever is longer.

6. Screening supine blood pressure ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. If blood pressure (BP) is ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated two more times and the average of the three BP values should be used to determine the subject's eligibility.

7. 12-lead ECG demonstrating QTc >450, or a QRS interval >120 msec at Screening. If QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated two more times and the average of the three QTc (or QRS) values should be used to determine the subject's eligibility.

8. Subjects 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:

   - Serum creatinine level above the upper limit of normal or an estimated Glomerular Filtration Rate (GFR) value ≤80 mL/min, based on the Cockcroft-Gault calculation, at Screening (see Appendix 2).

   - Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transminase (SGOT) or alanine aminotransferase (ALT)/serum glutamic pyruvic transminase (SGPT) ≥ values more than 1.5 times the upper limit of normal.

   - Fasting glucose >110 mg/dL.

   - Total bilirubin ≥1.5 x ULN.

   - A white blood cell count below $4.5x10^3/mm^3$, including history of benign ethnic neutropenia. Subjects with borderline clinical laboratory values outside the reference range may be included in the study if the investigator deems that the values are not clinically significant.

   - Absolute neutrophil count of $<2 \times 10^9/L$ ($<2000/mm^3$).

   - Hematocrit below 38% for males and 33% for females. Subjects with borderline clinical laboratory values outside the reference range may be included in the study if the investigator deems that the values are not clinically significant.

   - Red blood cell and reticulocytes outside the reference range at screening Subjects with borderline clinical laboratory values outside the reference range may be included in the study if the Investigator deems that the values are not clinically significant.

   - Platelet counts below LLN. Subjects with borderline clinical laboratory values outside the reference range may be included in the study if the investigator deems that the values are not clinically significant.

9. Any medical history of disease that has the potential to cause a rise in total bilirubin over the upper limit of normal (ULN). Subjects with borderline clinical laboratory values outside the reference range may be included in the study if the investigator deems that the values are not clinically significant.

   Note: Subjects 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.

10. Pregnant female subjects; breastfeeding female subjects; female subjects of childbearing potential.

11. Fertile male subjects who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product.

12. Herbal supplements and and hormone replacement therapy must be discontinued 28 days prior to the first dose of study medication. As an exception, acetaminophen/paracetamol may be used at doses of ≤1 g/day. Limited use of non-prescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor.

13. Use of prescription or nonprescription drugs and dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study medication. As an exception, acetaminophen/paracetamol may be used at doses of ≤1 g/day. Limited use of nonprescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case by case basis following approval by the sponsor.

14. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 56 days prior to dosing.

15. History of sensitivity to heparin or heparin-induced thrombocytopenia.

16. Unwilling or unable to comply with the Lifestyle Requirements (Section 4.6) described in this protocol.

17. Other severe 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 subject inappropriate for entry into this study.

18. Subjects who are 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 subjects who are Pfizer employees including their family members directly involved in the conduct of the study.

19. Will have vaccination with live virus, attenuated live virus, or any live viral components within the 6 weeks prior to the first dose of study drug or is to receive these vaccines at any time during treatment or within 8 weeks following completion of study treatment.

20. Have a history of any lymphoproliferative disorder (such as Epstein Barr Virus [EBV]-related lymphoproliferative disorder, as reported in some subjects on other immunosuppressive drugs), history of lymphoma, leukemia, myeloproliferative disorders, multiple myeloma, or signs and symptoms suggestive of current lymphatic disease.

21. Have a clinically significant infection currently or within 6 months of first dose of study drug (eg, those requiring hospitalization or parenteral antimicrobial therapy or opportunistic infections), or a history of chronic or recurrent infectious disease.

22. Have or have had symptomatic herpes zoster or herpes simplex within 12 weeks, more than one episode of local herpes zoster, or a history (single episode) of disseminated zoster.

23. Are known to be infected with human immunodeficiency virus (HIV) or hepatitis B or C viruses.

24. Subjects with a history of cancer with the exception of adequately treated basal cell or squamous cell carcinoma of the skin.

25. Acute disease state (eg, nausea, vomiting, fever, or diarrhea) within 7 days of Day 1.

26. Have a first-degree relative with a hereditary immunodeficiency.

27. Have undergone significant trauma or major surgery within 4 weeks of Screening.

28. Use of tobacco/nicotine containing products in excess of ≥5 cigarettes/day.

29. Consumption of grapefruit or grapefruit juice or citrus fruits eg, Seville oranges, pomelos within 7 days prior to the first dose of study medication until collection of the final pharmacokinetic blood sample.

30. Subjects who received (within 4 weeks of first dose of PF-06826647) or were likely to receive during the study any of the medications listed in protocol Appendix 3.

4.3. Inclusion Criteria: Psoriasis Multiple Dose Cohorts

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Female subjects of non-childbearing potential and/or male subjects with a diagnosis of plaque psoriasis who are between the ages of 18 and 65 years, inclusive.

2. Female subjects of non-childbearing potential must meet at least 1 of the following criteria:

   a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum FSH level confirming the post menopausal state.

   b. Have undergone a documented hysterectomy and/or bilateral oophorectomy.

   c. Have medically confirmed ovarian failure.

   All other female subjects (including females with tubal ligations) are considered to be of childbearing potential.

3. Body Mass Index (BMI) of 17.5 to 37.5 kg/m^2; and a total body weight >50 kg (110 lbs).

4. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.

5. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

6. Have a diagnosis of plaque psoriasis for at least 6 months prior to first study dose.

7. Have plaque-type psoriasis covering at least 15% of total BSA at Day -1 (prior to randomization in the study).

8. Have a PASI score of 12 or greater at Day -1 (prior to randomization in the study).

9. Be a candidate for phototherapy or systemic treatment of psoriasis (either naïve or history of previous treatment) in the opinion of the investigator.

10. Must agree to avoid prolonged exposure to the sun and avoid other ultraviolet light sources during the study (eg, tanning beds).

11. No evidence of active or latent or inadequately treated infection with Mycobacterium tuberculosis (TB) as defined by the following:

    a. negative Interferon Gamma Release Assay (IGRA) (with the following acceptable assays: QuantiFERON^{R}-TB Gold (QFT-G) test, T-SPOT TB, QuantiFERON-TB Gold In-Tube test (QFT-GIT)) performed during Screening or within 3 months prior to Day 1.

    AND

    b. No history of either untreated or inadequately treated latent or active TB infection.

    If a subject has previously received an adequate course of therapy for either latent (9 months of isoniazid in a locale where rates of primary multi-drug resistant TB infection are <5%) or active TB infection, a QFT Gold test need to be obtained, but a chest radiograph or other appropriate image negative for active TB infection, must still be obtained if not done so within the prior 3 months.

    A subject who is currently being treated for either latent or active TB infection is to be excluded.

4.4. Exclusion Criteria: Psoriasis Multiple Dose Cohort

Subjects presenting with any of the following characteristics/conditions will not be included in the study:

1. Currently have non-plaque forms of psoriasis, eg, erythrodermic, guttate, or pustular psoriasis.

2. Have 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.

3. If 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.

4. Subjects 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:

    a. Hemoglobin:

        - If the hemoglobin level is greater than 5% below the lower limit of normal (LLN), subject is to be excluded;

- If the hemoglobin level is within 5% below the LLN, iron and folate levels are to be measured: if iron and/or folate levels are below the LLN, subject is to be excluded.

b. Absolute neutrophil count of $<2 \times 10^9$/L ($<2000/mm^3$).

c. Platelet count below the LLN.

d. Serum creatinine level above the upper limit of normal or an estimated Glomerular Filtration Rate (GFR) value ≤80 mL/min, based on the Cockcroft-Gault calculation, at Screening (see Appendix 2).

e. Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transminase (SGOT) or alanine aminotransferase (ALT)/serum glutamic pyruvic transminase (SGPT) ≥ values more than 1.5 times the upper limit of normal.

f. Fasting glucose >140 mg/dL.

g. Total bilirubin ≥1.5 x ULN; subjects 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.

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

- 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) (Appendix 9).

- 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.

- Any lifetime history of serious or recurrent suicidal behavior.

- Suicidal behaviors questionnaire –revised (SBQ-R) (Appendix 10) total score ≥8.

- Clinically significant depression: patient health questionnaire – 8 items (PHQ-8) (Appendix 11) when the total score ≥15.

- The presence of any current major psychiatric disorder that is not explicitly permitted in the inclusion/exclusion criteria.

- In the opinion of the investigator or Pfizer (or designee) exclusion is required.

6. Have current or recent history of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiac, neurological or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at time of dosing).

7. Will have vaccination with live virus, attenuated live virus, or any live viral components within the 6 weeks prior to the first dose of study drug or is to receive these vaccines at any time during treatment or within 8 weeks following completion of study treatment.

8. Will have routine household contact with individuals who have received vaccination with live virus, or attenuated live virus, for 8 weeks following completion of study treatment.

9. Have a history of any lymphoproliferative disorder (such as Epstein Barr Virus [EBV]-related lymphoproliferative disorder, as reported in some subjects on other immunosuppressive drugs), history of lymphoma, leukemia, myeloproliferative disorders, multiple myeloma, or signs and symptoms suggestive of current lymphatic disease.

10. Have a clinically significant infection currently or within 6 months of first dose of study drug (eg, those requiring hospitalization or parenteral antimicrobial therapy or opportunistic infections), or a history of chronic or recurrent infectious disease.

11. Have or have had symptomatic herpes zoster or herpes simplex within 12 weeks, more than one episode of local herpes zoster, or a history (single episode) of disseminated zoster.

12. Any prior treatment with lymphocyte depleting agents/therapies (such as CamPath® [alemtuzab], alkylating agents [eg, cyclophosphamide or chlorambucil],total lymphoid irradiation, etc).

13. Have any condition possibly affecting oral drug absorption, gastrectomy, or clinically significant diabetic gastroenteropathy.

14. History of regular alcohol consumption exceeding 7 drinks/week for females or 14 drinks/week for males (1 drink = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor) within 6 months of Screening.

15. 12-lead ECG demonstrating QTc >450, or a QRS interval >120 msec msec at Screening. If QTc exceeds 450 msec or QRS exceeds 120 msec, the ECG should be repeated two more times and the average of the three QTc (or QRS) values should be used to determine the subject's eligibility.

16. Screening supine blood pressure ≥160 mm Hg (systolic) or ≥100 mm Hg (diastolic), following at least 5 minutes of supine rest. If blood pressure (BP) is ≥160 mm Hg (systolic) or ≥100 mm Hg (diastolic), the BP should be repeated two more times and the average of the three BP values should be used to determine the subject's eligibility.

17. Herbal supplements and and hormone replacement therapy must be discontinued 28 days prior to the first dose of study medication. As an exception, acetaminophen/paracetamol may be used at doses of ≤1 g/day. Limited use of non-prescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor.

18. Donated blood in excess of 500 mL (excluding plasma donations) within 2 months prior to the first dose of study drug.

19. Acute disease state (eg, nausea, vomiting, fever, or diarrhea) within 7 days of Day 1.

20. Have a first-degree relative with a hereditary immunodeficiency.

21. Have any malignancies or have a history of malignancies with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin.

22. Have undergone significant trauma or major surgery within 4 weeks of Screening.

23. Are known to be infected with human immunodeficiency virus (HIV) or hepatitis B or C viruses.

24. Have participated in any other studies with JAK inhibitors within 3 months prior to dosing.

25. In the opinion of the investigator or Pfizer, will be uncooperative or unable to comply with study procedures.

26. Have participated in other studies involving investigational drug(s) within 30 days or 5 half-lives (whichever is longer) prior to study entry and/or during study participation.

27. 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 subject inappropriate for entry into this study.

28. Have any other condition which would make the subject unsuitable for inclusion in the study.

29. Subjects who are 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 subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.

30. Pregnant female subjects; breastfeeding female subjects; female subjects of childbearing potential.

31. Fertile males subjects who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product.

32. Use of tobacco/nicotine containing products in excess of ≥5 cigarettes/day.

33. A positive urine drug screen.

34. Consumption of grapefruit or grapefruit juice or citrus fruits eg, Seville oranges, pomelos within 7 days prior to the first dose of study medication until collection of the final pharmacokinetic blood sample.

35. Require treatment with prohibited concomitant medication(s) listed in Appendix 3 or have received a prohibited concomitant medication in the 4 weeks prior to the first dose of study drug. Subjects 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 2 weeks or 5 half-lives (whichever is longer) prior to first dose of study drug.

36. Have previously been treated with efalizumab (Raptiva®).

37. Have previously been treated with secukinumab (Cosentyx) or ixekizumab (Taltz).

38. Have previously been treated with ustekinumab (Stelara®).

39. Have received any of the following treatment regimens specified in the timeframes outlined below:

    Biologic therapies for psoriasis (including brodalumab) have discontinuation periods determined from approximately 5x half-life of the respective biologic.

    Within 12 weeks of first dose of study drug:

    - Any experimental therapy for psoriasis, psoriatic arthritis, or rheumatoid arthritis.

Exception: Investigational biologics should be discussed with the Pfizer Medical Monitor (or designee) to confirm period of discontinuation required.

- Apremilast (Otezla).

Within 10 weeks of first dose of study drug:

- Adalimumab (Humira®);
- Certolizumab pegol (Cimzia®);
- Infliximab (Remicade®);
- Alefacept (Amevive®).

Within 4 weeks of first dose of study drug:

- etanercept (Enbrel®).
- Systemic treatments other than biologics that could affect psoriasis (eg, oral or injectable corticosteroids, retinoids, methotrexate, cyclosporine, fumaric acid derivatives, sulfasalazine, hydroxycarbamide (hydroxyurea), azathioprine).
- Phototherapy and psoralens (PUVA).
- Other – intramuscular gold, herbal medications.

Within 2 weeks of first dose of study drug:

- Topical treatments that could affect psoriasis (eg, corticosteroids, tars, keratolytics, anthralin, vitamin D analogs, and retinoids). Treatments allowed are: non-medicated emollients for use over the whole body, low or least potent(Class 6 or 7) topical corticosteroids for the palms, soles, face, andintertriginous areas only; tar and salicylic acid preparations for the scalp only, or shampoos free of corticosteroids for the scalp only. More potent topical steroids (Class 5-2) could be considered on an as-needed basis on the face, scalp, and genital areas only after discussion with the Sponsor's Medical Monitor.
- Phototherapy with UVB (narrowband or broadband).

4.5. Randomization Criteria

Subjects will be randomized into the study provided they have satisfied all subject eligibility criteria.

Healthy subjects will be randomized (once) into the SAD period, at which time, they will receive treatment assignment (active PF-06826647 dose level or placebo) for both the SAD and MAD periods. Subjects will receive the same blinded treatment assignment (ie, the same

dose level of active PF-06826647 or placebo) throughout in both the SAD (Period 1) and MAD (Period 2) periods. Optional BID cohort subjects may be directly randomized to the twice daily 10 day treatment regimen once confirmation of eligibility criteria occurs, without the need to participate in a single dose period.

- The randomization ratio for the cohorts in the healthy subject SAD/MAD segment will be 3: 1 (PF-06826647:Placebo).

- The randomization ratio for the planned psoriasis multiple dose cohorts will be 2:1 (PF-06826647:Placebo).

4.6. Lifestyle Requirements

The following guidelines are provided:

4.6.1. Meals and Dietary Requirements

- Administration of investigation product will be in fasted state in SAD period and under standard meal condition in MAD (QD and BID) period and in Psoriasis cohorts. Based on the emerging PK, CCI and safety data, the meal condition requirement in SAD, MAD and Psoriasis cohorts may be adjusted.

- Under any meal condition, subjects will not be allowed to eat or drink grapefruit or grapefruit-related citrus fruits (eg, Seville oranges, pomelos) from 7 days prior to the first dose of study medication until collection of the final pharmacokinetic blood sample.

- Except when the investigational product is dosed under high fat meal condition, the total daily nutritional composition should be approximately 55% carbohydrate, 30% fat and 15% protein and the daily caloric intake per subject should not exceed approximately 3200 kcal while confined.

Dosing under fasted condition:

- Subjects must abstain from all food and drink (except water) at least 8 hours prior to any safety laboratory evaluations (as indiated in the study Schedule of Activities) and 8 hours prior to the collection of the pre-dose pharmacokinetic sample. Water is permitted until 1 hour prior to investigational product administration.

- The investigational product should be administered with approximately 240 mL (8 fluid ounces) of ambient temperature water. Additional water may be allowed if needed to administer the entire dose.

- Water may be consumed without restriction beginning 1 hour after dosing. Non-caffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices – see above) may be consumed with meals and the evening snack.

- Lunch will be provided approximately 4 hours after dosing.

- Dinner will be provided approximately 9 to 10 hours after dosing.

- An evening snack may be permitted.

Dosing under standard meal condition:

Following an overnight fast of at least 8 hours, subjects should start breakfast approximately 25 minutes prior to the morning administration of the investigational product when dosing in the fed condition. In BID cohort, subjects should start dinner approximately 25 minutes prior to the evening administration of the investigational product, when dosing in the fed condition. The breakfast and dinner (BID period only) will be consumed over approximately 20 minutes with study drug administered within approximately 5 minutes after completion of the meal. Subjects will be encouraged to eat the full standard meal on PK profile assessment days (Days 1 and 10) and are required to eat a minimum of approximately 80% of the meal preceding dosing. Subjects will be encouraged to eat the full standard meal and are required to eat a minimum of approximately 50% of the meal on all other dosing days. Subjects should be encouraged to eat any snack that will precede dosing. The study treatment should be administered with approximately 240 mL (8 fluid ounces) of ambient temperature water. Additional water may be allowed if required to administer the entire dose. No food will be allowed for at least 2 hours post-dose.

- Water can be allowed as desired except for 1 hour after investigational product administration. There are no water restrictions prior to dosing for subjects dosed under fed conditions.

- Lunch will be provided approximately 4 hours after dosing.

- Dinner will be provided approximately 9 to 10 hours after dosing.

- An evening snack may be permitted.

Dosing under high fat meal condition (if needed):

- Following an overnight fast of at least 8 hours, subjects should start a high-fat/high-calorie breakfast approximately 25 minutes prior to administration of the investigational product. The breakfast will be consumed over approximately 20 minutes with investigational product administered within approximately 5 minutes after completion of the meal. Subjects will be encouraged to eat the full meal on Day 1 and are required to eat a minimum of approximately 80% of the meal.

    - The study treatment should be administered with approximately 240 mL (8 fluid ounces) of ambient temperature water. Additional water may be allowed if required to administer the entire dose.

- The breakfast will be a high-calorie/high-fat test meal. The following breakfast as a representative example of a high-fat, high-calorie meal: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, 8 fluid ounces (240 mL) of whole milk.

- Water can be allowed as desired except for 1 hour after investigational product administration. There are no water restrictions prior to dosing for subjects dosed under fed conditions.

- The investigational product should be administered with approximately 240 mL of ambient temperature water.

- No food will be allowed for at least 2 hours post-dose.

- Lunch will be provided approximately 4 hours after dosing.

- Dinner will be provided approximately 9 to 10 hours after dosing.

- An evening snack may be permitted.

4.6.2. Alcohol, Caffeine, and Tobacco

- Subjects will abstain from alcohol for 24 hours prior to admission to the CRU and continue abstaining from alcohol until collection of the final pharmacokinetic sample of each study period. Subjects may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

- Subjects will abstain from caffeine-containing products for 24 hours prior to the start of dosing until collection of the final pharmacokinetic sample of each study period.

- Subjects will limit the use of tobacco- or nicotine-containing products for 24 hours prior to dosing and during confinement in the research unit to not exceed 5 cigarettes a day.

4.6.3. Activity

4.6.3.1. Healthy Volunteer Single Ascending Dose Period

- Subjects will be confined to the procedure room after dosing on Day 1 during continuous cardiac monitoring, except to use the bathroom. After this, if the equipment setup allows, subjects may be ambulatory during the ECG monitoring period, but should not engage in strenuous activities. If equipment does not allow ambulation, appropriate accommodations will be made by the study site to facilitate continuous monitoring (ie, bedside urinals should be provided to accommodate subjects' excretory needs).

4.6.3.2. All Subjects

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

- Subjects must avoid prolonged exposre to the sun and other ultravoilet light sources during this study (eg, tanning beds).

4.6.4. Contraception

All fertile male subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy, with their partner(s), must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of investigational product. The investigator or his/her designee, in consultation with the subject, will confirm the subject has selected the most appropriate method of contraception for the individual subject and his female partner from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently.

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the subject or male subject's female partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the postvasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

All sexually active male subjects must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 28 days after the last dose of PF-06826647.

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

4.6.4.1. Females – Childbearing Potential

Females of childbearing potential will be excluded from this study.

4.7. 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 team SharePoint site.

http://ecf.pfizer.com/sites/crops/team/C2501001/default.aspx

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study 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 subject'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. For sites other than a Pfizer CRU, the contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational product(s) PF-06826647 and matching placebo will be supplied as an extemperaneous preparation and tablets.

5.1. Allocation to Treatment

The investigator will assign subject numbers sequentially to the subjects as they are screened for the study. Pfizer will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the subject will receive the study treatment regimen assigned to the corresponding randomization number. It will also appear on the study medication containers.

Randomization will occur for the SAD/MAD cohorts, and the Psoriasis cohorts.

Healthy subjects will be randomized (once) into the SAD period, at which time, they will receive treatment assignment (active PF-06826647 dose level or placebo) for both the SAD and MAD periods. Subjects will receive the same blinded treatment assignment (ie, the same dose level of active PF-06826647 or placebo) throughout in both the SAD (Period 1) and MAD (Period 2) periods.

5.2. Breaking the Blind

This study will be subject and investigator blinded, sponsor-open. At the initiation of the study, the study site will be instructed on the method for breaking the blind. The method will be manual. Blinding codes should only be broken in emergency situations for reasons of subject safety. Whenever possible, the investigator or sub investigator should consult with a member of the study team prior to breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the case report form.

Blood specimens will be obtained from all subjects for pharmacokinetic analysis to maintain the study blind at the investigator site. For the SAD/MAD cohorts only the investigator site(s) and the study monitor(s) will be blinded to study treatment. A designated limited number of sponsor colleagues within the study team will be unblinded to subject treatments in order to permit real-time interpretation of the safety and PK data; and provide information necessary to potentially alter the dose-escalation sequence. The study monitor will remain blinded to treatment until all monitoring for the study has been completed. Specimens from subjects randomized to placebo will not be routinely analyzed. To minimize the potential for bias, treatment randomization information will be kept confidential by Pfizer personnel and will not be released to the investigator or investigator site personnel until the study database has been locked. If an investigator would like to know the treatment assignment of a subject in the case of emergencyor in the event of a safety concern, in which case, the process for breaking the blind must be followed.

The study will be double-blind (including site, investigator, subject), sponsor-open, for the Psoriasis cohorts. To minimize the potential for bias, treatment randomization information will be kept confidential and will not be released to the investigator or investigator site personnel until the study database has been locked. A designated limited number of Pfizer personnel will be unblinded to individual psoriasis subject treatment assignment to permit interpretation of interim analysis results, safety data, or management of subject's safety.

Site pharmacy staff involved in dose preparation will be unblinded. There may be one designated unblinded study monitor to perform drug accountability and site pharmacy monitoring activities.

5.3. Subject Compliance

Investigational product will be administered under the supervision of investigator site personnel. The oral cavity of each subject will be examined following dosing to assure investigational product was taken.

5.4. Investigational Product Supplies.

5.4.1. Dosage Form and Packaging

PF-06826647 will be supplied by Pfizer as 5 mg, 25 mg, or 100 mg tablets, and will be administered to healthy volunteers during the SAD/MAD periods and to psoriasis subjects.

All tablets will be supplied to the CRU in bulk. Individual dosing containers for unit dosing may be supplied, if needed.

There is no 3 mg tablet currently available. Therefore, PF-06826647 spray dried dispersion suspension will be administered to the first SAD cohort. Materials for PF-06826647 spray dried dispersion suspension and placebo dosages will be provided by Pfizer as bulk powders for extemporaneous preparation at the Clinical Research Unit (CRU), for administration to healthy subjects participating in the starting dose cohort (3 mg) of the Single Ascending Dose portion of the protocol.

5.4.2. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the investigational product ready for administration or dispensing to the subject/caregiver by qualified staff. Dispensing is defined as the provision of investigational product, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider, subject, or caregiver in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

PF-06826647 and placebo oral dosing suspensions will be prepared in the CRU by 2 qualified, unblinded operators, one of whom is a pharmacist. Details of dose preparation will be given in a separate Extemporaneous Dispensing Record (EDR). Prepared doses will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the investigator site's labeling requirements.

PF-06826647 and placebo tablets will be prepared for dosing at the CRU in the individual dosing containers by 2 qualified, unblinded operators, one of whom is a pharmacist. The tablets will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

5.5. Administration

Following an overnight fast of at least 8 hours, subjects will receive study medication at approximately 08:00 hours (plus or minus 2 hours). Investigator site personnel will administer study medication to subjects.

For subjects undergoing BID dosing, the second dose of study medication will be administered approximately 12 hours after the initial (morning) dose.

Blinded PF-06826647 tablets and matching placebo will be provided as tablets for oral administration. The PF-06826647 5 mg, 25 mg, and 100 mg tablets and their matching placebos will be supplied in bottles and labeled according to local regulatory requirements.

Subjects who receive tablet formulation of PF-06826647, will be instructed to swallow the study medication whole, and not to manipulate or chew the medication prior to swallowing. Subjects will be instructed to swallow with ambient water to a total volume of 240 mL. Additional water is allowed if needed to complete administration of the entire dose. No EDR will be provided for the tablet administration.

Administration instructions for the PF-06826647 suspension dose (3 mg single dose cohort only) will be provided in the extemporaneous dispensing record.

In order to standardize the conditions on pharmacokinetic sampling days, all subjects will be required to refrain from lying down (except when required for blood pressure, pulse rate, and ECG measurements). Meal and dietary requirements as described in Section 4.6.1 should be followed.

5.6. Investigational Product Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products, including excipients, or drug substance are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products, excipients or drug substance should be stored in their original containers and in accordance with the labels. See the EDR or label for storage conditions of the excipients, drug substance or product once constituted.

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

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last

evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature-monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product-label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

5.7. 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.

5.7.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (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 Pfizer, and all destruction must be adequately documented.

5.8. Concomitant Treatment(s)

Subjects will abstain from all concomitant treatments, except for the treatment of adverse events, as described in the Exclusion Criteria section and in Appendix 3 of this protocol.

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant treatment at clinic visit as indicated in the Schedule of Activities.

Treatments taken within 28 days before the first dose of investigational product will be documented as a prior treatment. Treatments taken after the first dose of investigational product will be documented as concomitant treatments.

Females taking hormone replacement therapy may be eligible to participate in this study if they are willing to discontinue therapy at least 28 days prior to the first dose of study treatment and remain off hormonal therapy for the duration of the study.

6. STUDY PROCEDURES

6.1. Screening

For screening procedures, see Schedule of Activities and ASSESSMENTS section.

Subjects will be screened within 28 days prior to administration of the study medication to confirm that they meet the subject selection criteria for the study. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from each subject in accordance with the procedures described in the protocol. If the time between Screening and dosing for a healthy subject in the SAD period is anticipated to exceed 28 days as a result of unexpected delays (eg, delayed drug shipment), then subjects do not require re-screening if the Day -1 laboratory (including urine drug screen), ECG, vital sign results, contraception check and urine pregnancy test (if applicable), and review of prior/concomitant medications all confirm that the subject still meets the eligibility criteria, as outlined in Section 4 of Protocol C2501001.

A healthy subject who qualified for this protocol but did not enroll from an earlier cohort may participate in a subsequent cohort without re-screening provided the Day -1 laboratory (including urine drug screen), ECG, vital sign results, contraception check and urine pregnancy test (if applicable) and review of prior/concomitant medications all confirm that the subject still meets the eligibility criteria outlined in Section 4 of protocol C2501001. In addition, other clinical assessments or specimen collections may be used without repeat collection, as appropriate following discussion with Sponsor medical monitor.

If needed, eligible psoriasis subjects who have completed screening procedures but did not enroll due to scheduling related delays, site logistics, or Sponsor imposed delays (eg, due to protocol amendments or other), the screening window may be extended from 28 days as described above, to up to 45 days.

6.2. Treatment Period

For treatment period procedures, see Schedule of Activities and ASSESSMENTS section.

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6.3. Follow-up/End of Study Procedures

For follow up and end of study procedures, see Schedule of Activities and ASSESSMENTS section.

6.3.1. Follow-up Contact

Follow-up contact will be completed at least 28 calendar days and up to 35 calendar days after the last administration of the investigational product to capture any potential adverse events (see the Time Period for Collecting AE/SAE Information section) and to confirm

appropriate contraception usage (see the Contraception section). Contact with the subject may be done via a phone call.

6.4. Subject Withdrawal/Early Termination

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal From the Study Due to Adverse Events section) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given investigator site. The early termination visit applies only to subjects who are randomized and then are prematurely withdrawn from the study.

It may be appropriate for the subject to return to the clinic for final safety assessments to be scheduled as early as practically feasible following the decision to withdraw from the study. Subjects should be questioned regarding their reason for withdrawal. At the early withdrawal visit, every effort must be made to complete the following assessments:

- Physical examination;
- Supine blood pressure and pulse rate measurements and oral temperature;
- 12-lead ECG measurement;
- Blood and urine specimens for safety laboratory;
- Blood sample for pharmacokinetic analysis *.

* For subjects who discontinue early during the treatment period due to an adverse event, a final PK sample should be collected when possible. Subjects discontinuing early for other reasons may not be asked to provide a final PK sample, depending on when in the study discontinuation occurs. For such cases, please contact the study sponsor for further guidance.

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

Subjects who withdraw from the study may be replaced at the discretion of the investigator upon consultation with the sponsor (provided the nature of the safety event does not preclude dose escalation and exposure stopping limits are observed).

Replacement of psoriasis subject(s) who discontinue early may occur at discretion of the sponsor in order to ensure adequate number of subjects completing through Day 28.

Withdrawal of consent:

Subjects who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects 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 case report form (CRF) page. In the event that vital status (whether the subject 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.

If the subject withdraws from the study and also withdraws consent 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.

Lost to follow-up:

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. The investigator or site staff should attempt to contact the subject twice. After 2 attempts, CRU staff may send a registered letter. If no response is received from the subject, the subject will be considered lost to follow-up. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

7. ASSESSMENTS

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 subject. 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.

7.1. Safety

7.1.1. Laboratory Tests

The following safety laboratory tests will be performed at times defined in the STUDY PROCEDURES 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 labs may be obtained at any time during the study to assess any perceived safety concerns.

Table 7. Laboratory Tests

Hematology	Chemistry	*Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs) Reticulocytes (%)	BUN/urea and Creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (Bicarbonate) AST, ALT Total Bilirubin Alkaline phosphatase Uric acid Albumin Total protein Serum Cystatin C Creatinine phosphokinase (for psoriasis subjects only)	pH Glucose (qualified) Protein (qualified) Blood (qualified) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	FSH[b] Urine drug screening[c] CCI Fibrinogen Lipids: TC, TG, LDLc, HDL Interferon Gamma Release Assay (IGRA) (with the following acceptable assays: QuantiFERON®-TB Gold (QFT-G) test, T-SPOT TB, QuantiFERON-TB Gold In-Tube test (QFT-GIT)[f] HIV, HepBsAg, HepBcAb, HCVAb[f] CCI PK 6β-hydroxy cortisol CCI CCI
	Additional Tests[e] (Needed for Hy's law)	Other :	
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT PT/INR Total bile acids Acetaminophen drug and/or protein adduct levels	Urine for 24 hour creatinine clearance and CCI	

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

b. At Screening only, in females who are amenorrheic for at least 12 consecutive months.

c. At Screening and pre-dose only (see Schedule of Activities). Minimum requirement for drug testing includes: cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines and amphetamines.

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e. Additional testing for potential Hy's Law cases only.

f. Screening only. All subjects will be screened for HBsAg and HBcAb; subjects who are HBsAg positive will be screen-failed. Subjects who are HBsAg negative but HBcAb positive will be reflex-tested for HBsAb and, if HBsAb positive, may enroll; if HBsAb negative, they will be screen-failed. Subjects who are positive for HCV Ab or HIV will be screen-failed.

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* Urinalysis sample may also be used to assess additional markers of renal function.

This table lists all protocol laboratory tests included in the study. For a detailed description of laboratory tests required for a given subject cohort with specific collection time points, please refer to the Schedule of Activities.

- Minimum requirement for drug testing includes: cocaine, THC, opiates/opioids, benzodiazepines and amphetamines.

- Subjects may undergo random urine drug screening at the discretion of the investigator. Drug screening conducted prior to dosing must be negative for subjects to receive study medication.

7.1.2. Pregnancy Testing

All pregnancy tests used in this study, either urine or serum, must have a sensitivity of at least 25 mIU/mL and must be performed by a certified laboratory. For female subjects of childbearing potential, 2 negative pregnancy tests are required before receiving investigational product/study treatment(s) (1 negative pregnancy test at screening and 1 at the baseline visit immediately before investigational product/study treatment administration). Following a negative pregnancy test result at screening, appropriate contraception must be commenced and the second negative pregnancy test result will then be required at the baseline visit and within 5 days after the first day of the menstrual period (counting the first day of the menstrual period as Day 1) before the subject may receive the investigational product/study treatment. In the absence of regular menstrual bleeding, the study candidate should have used 2 forms of contraception for at least 1 month before the second pregnancy test. Pregnancy tests will also be repeated at every visit and at the end of the study to confirm that the subject has not become pregnant during the study. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period and when potential pregnancy is otherwise suspected, and may be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product and from the study.

7.1.3. Physical Examinations

Physical examinations may be conducted by a physician, trained physician assistant, or nurse practitioner as acceptable according to local regulation. A full physical examination will include head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, and neurological systems. The limited or abbreviated physical examination will be focused on general appearance, the respiratory and cardiovascular systems, as well as towards subject reported symptoms.

For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Subjects must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

7.1.4. Blood Pressure and Pulse Rate

Blood pressure and pulse rate will be measured at times specified in Schedule of Activities section of this protocol. Additional collection times, or changes to collection times of blood pressure and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

Supine blood pressure will be measured with the subject's arm supported at the level of the heart and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. Subjects should be instructed not to speak during measurements.

The same properly sized and calibrated blood pressure cuff will be used to measure blood pressure each time. The use of an automated device 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, blood pressure and pulse rate should be obtained prior to the nominal time of the blood collection.

For current smokers participating in this study, vital sign assessment (blood pressure and pulse rate) should not occur within 1 hour of smoking.

7.1.5. Temperature

Temperature will be measured orally. No eating, drinking or smoking is allowed for 15 minutes prior to the measurement.

7.1.6. Electrocardiogram

Electrocardiograms (ECGs) should be collected at times specified in the Schedule of Activities section of this protocol.

All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position.

Triplicate 12-lead ECGs will be obtained approximately 2-4 minutes apart; the average of the triplicate ECG measurements collected predose on Day 1 will serve as each subject's baseline QTc value. When the timing of these measurements coincides with a blood collection, the ECG should be obtained prior to the nominal time of the blood collection, blood pressure and pulse rate.

To ensure safety of the subjects, a qualified individual at the investigator site will make comparisons to baseline measurements. Within a given study period (ie, SAD, MAD), baseline measurements from the current period will be used for comparison. If the QTc interval is increased by ≥45 msec from the baseline, or an absolute QTc value is ≥500 msec for any scheduled ECG, then 2 additional ECGs will be collected, approximately 2-4 minutes apart, to confirm the original measurement. If either of the QTc values from these repeated ECGs remains above the threshold value (≥45 msec from the baseline; or is ≥500 msec), then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If the average of QTc values from the triplicate measurements remains above the threshold value (≥45 msec from the baseline; or is ≥500 msec), then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If QTc values remain ≥500 msec (or ≥45 msec from the baseline) for greater than 4 hours (or sooner at the discretion of the investigator); or QTc intervals get progressively longer, the subject should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than 500 msec (or to <45 msec above the baseline) 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 are 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 physician's interpretation determines that the QTc values are in the acceptable range.

For current smokers participating in this study, ECG assessments should not occur within 1 hour of smoking.

7.1.7. Continuous Cardiac Monitoring by Telemetry

Continous telemetry monitoring will be conducted in the single ascending dose period only.

All abnormal rhythms will be recorded and reviewed by the study physician for the presence of rhythms of potential clinical concern. The time, duration, and description of the clinically significant event will be recorded in the case report form (CRF). In addition, a printed record of the tracing(s) of the clinically significant rhythm(s) will be made and retained with other source documents.

Telemetry should be collected using a centralized system that also allows for the storage and advanced analysis of all recorded data in order to preserve important events for future evaluations. Holter monitoring should not be used in parallel with continuous telemetry, unless it is the only means of data storage available at the investigator site, or verifiable arrhythmia quantification is required. To establish a baseline, telemetry should be recorded for at least 2 hours before dosing in Period 1, single ascending dose period. This may be done -2 hours immediately prior to dosing or at some 2-hour continuous interval in the 24 hours prior to dosing, as long as the recording is performed when the subject is awake. Telemetry may be stopped within a reasonably short period of time prior to dosing, in order to avoid interference with study operations conducted immediately before dosing. However, it is expected that the telemetry leads will be in place and the system connected prior to dosing.

Continuous cardiac monitoring by telemetry will be conducted 15 minutes pre dose through the 8 hour post dose period, during the single ascending dose period.

7.1.8. Chest Radiograph

Potential psoriasis subjects will have a standard chest radiograph performed as part of Screening if the individual previously received an adequate course of therapy for either latent (9 months of isoniazid in a locale where rates of primary multi-drug resistant TB infection are <5%) or active TB infection, and if there is no record and no report of having one performed in the prior 3 months.

7.1.9. Interferon Gamma Release Assay (IGRA) Tests

Interferon Gamma Release Assay (IGRA) will be performed at screening. The following acceptable IGRA assays include: Interferon Gamma Release Assay (IGRA) (with the following acceptable assays: QuantiFERON^{R}-TB Gold (QFT-G) test, QuantiFERON-TB Gold In-Tube test (QFT-GIT) and T-SPOT TB test). A QFT-G test is recommended in subjects who have been previously vaccinated with BCG.

7.1.10. Urine Creatinine and [redacted]

CCI [redacted]

7.1.10.2. 24 Hour Urine Creatinine and CCI [redacted] in Multiple Ascending Dose Period: Day -1 and Day 10

The same procedure outlined in Section 7.1.10.1 for urine collection in the single ascending dose period will be utilized in the multiple ascending dose period. One aliquot of 10 mL ("urine blank") from the 0-24 hour period will be obtained from the urine collection for creatinine measurement on Day -1. Also, two 1-mL aliquots will be transferred to appropriately-labeled tubes and stored at -70°C within 2 hours of collection for CCI [redacted]

After 24-hour collection on Day 10, two aliquots of 10 mL will be collected in appropriately labelled tubes for PK analysis and creatinine measurement. Also, two 1-mL aliquots will be transferred to appropriately-labeled tubes and stored at -70°C within 2 hours of collection for CCI [redacted]

On Day 10, urine will be collected from the BID period over 2 time intervals: 0-12 hours and 12-24 hours. The PK sample will be collected from the 0-12 hour interval.

CCI [redacted]

7.1.10.3. 24 Hour Creatinine Clearance Calculation

Creatinine clearance (mL/min) = (Creatinine (urine)/Creatinine(serum)) x (Volume Urine (mL)/Time (hours) x 60)

CCI [redacted]

7.1.11. Serum Creatinine and Serum Cystatin-C

Serum creatinine is the best known standard test for monitoring renal function. However, serum creatinine based estimates of glomerular filtration rate (eGFR) may be affected by factors other than renal function, including chronic and acute illness. Cystatin C is a test that can be used either as an adjunct to or a replacement for serum creatinine. The most reliable estimates of GFR use both test results.[8]

Cystatin C is a low molecular weight protein that is used as an alternative to serum creatinine for monitoring of renal function. It seems to correlate more closely with GFR than does serum creatinine concentration and may be a more sensitive detector of early renal dysfunction.[9,10] While use of cystatin C has been limited, its independence of demographic

factors (eg, race) has made it an interesting means of determining changes in renal function in clinical settings and it is included in the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. Estimated GFR may be calculated via the 2012 Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) creatinine, cystatin C, or creatinine-Cystatin C equations.[11]

Serum creatinine and serum cystatin C will be measured from the serum chemistry specified in the Schedule of Activities section of the protocol. Serum creatinine and cystatin C based eGFR will be calculated at baseline and end of treatment (EOT) at a minimum (additional time points may be assessed).

When a subject has an increase in serum creatinine of ≥0.3 mg/dL relative to the subject's baseline, and after that increase has been confirmed by a (single) repeat test obtained as soon as practically feasible, but within 24 hours of the initial result, this will trigger assessment of serum cystatin-C in order to facilitate both cystatin C based and serum creatinine based eGFR calculations.

7.1.12. Estimated Glomerular Filtration Rate

Serum creatinine and serum cystatin-C based estimated GFR (eGFR) will be calculated at baseline and end of study treatment period at a minimum for all subjects, in order to facilitate calculation of eGFR at these time points. When cystatin-C testing is performed during the treatment period, corresponding serum creatinine and cystatin-C based eGFR will be determined to support assessment of renal function.

The respective estimated GFR (eGFR) values will be calculated using the 2 sets of equations developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), which utilize serum creatinine (SCr) and serum Cystatin C (S Cystatin C) respectively.[7] (Appendix 4).

7.2. Selection of IndexPlaques and Non-Lesional Skin for Skin Biopsies for Psoriasis Subjects

The index psoriatic plaque(s) to be used for skin biopsy should be selected pre-dose at the Day -1 visit.

Index lesion sites may be located on the torso (upper and mid back, chest), abdomen, buttocks, upper arms, and upper legs. Index lesions may not be located on the scalp, face, elbows, knees, lower legs, genital area and inguinal area, intertriginous areas and lower back.

Ideally, a single target plaque, approximately the size of the palm of the subject's hand, should be identified and the location and borders noted in the clinic chart; anatomical markers should be used as needed to describe the target plaque location. A photograph of the site may also be used. The plaque should be of sufficient size that the presence of multiple biopsy sites will not interfere with clinical evaluation of the lesion; potential biopsy sites should be pre-selected. The plaque should also be large enough to perform the required number of biopsies specified in the protocol. If a single index lesion meeting the above description cannot be found, two index plaques, located in the same area of the body, that are

at least 3 to 5 cm in diameter should be identified and the locations noted in the clinic chart. The index plaque(s) must have a total score of at least 5 CCI [redacted] and a score of at least 2 for induration at the time of pre-dose assessment. The plaques selected should have a similar appearance of severity, ie, plaques should be similar with regard to degree of erythema, induration and scaling.

An area of non-lesional skin anatomically similar in location to the target plaque should also be selected for biopsy. The selected non-lesional skin area should be at least 3 cm from the target psoriatic plaque. A biopsy of non-lesional skin will be obtained pre-dose at the Day -1 visit only.

7.3. Skin Biopsies (Psoriasis Subjects only)

The index plaque(s) selected for biopsy will be outlined using a black permanent marker on plastic transparency film. An area will be marked on the transparency film for identification and biopsy. The film will be identified with the study number and subject's identification number and retained with subject's clinic/site source documents.

Punch biopsies of the lesional skin will be obtained at each time point as specified in the Schedule of Activities. At the discretion of the investigator and the subject, two 4 mm biopsies will be obtained. At Day -1, two 4 mm biopsies of lesional skin and two 4 mm biopsies of non-lesional skin will be obtained.

Biopsy samples will be prepared and shipped following instructions in a separate manual provided by the sponsor.

Throughout the study period, the 'punch' biopsy instrument should be placed at least 3 mm from the target plaque's edge as identified at the Day -1 Visit.

Any two biopsy sites will be at least the width of the biopsy punch instrument apart.

CCI [redacted]

Punch biopsies from the index psoriatic plaque(s) will be obtained pre-dose on Day -1, at Day 14 and pre-dose at Day 28. Punch biopsy sampling of normal non-lesional skin will be obtained pre-dose at the Day -1 visit only. The biopsies may be used for RNA, protein and immunohistochemical analysis.

The shipment address and laboratory contact information will be provided to the investigator prior to initiation of the study. Details on the procedure for skin biopsy and sample preparation will be provided to investigators in a separate manual.

CCI [redacted]

[redacted]

As skin biopsies may be associated with risk of bleeding or infection, subjects will be instructed to contact the investigator or other designated site staff if they experience bleeding, warmth, swelling, tenderness, or erythema at the biopsy site; an unscheduled visit may be required for clinical assessment.

7.4. Psoriasis Clinical and Histological Assessments

Clinical and histological psoriasis assessments that will be collected throughout the study are outlined in this section. These measures will be evaluated by an experienced physician, or qualified medical professional. Detailed descriptions for the CCI [redacted], CCI [redacted], and Patient Global Assessment are provided in the Appendices.

7.4.1. Psoriasis Area and Severity Index (PASI) (Psoriasis subjects only)

PASI should be collected at times specified in the Schedule of Activities section of this protocol.

The Psoriasis Area and Severity Index quantifies the severity of a subject'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.

CCI [redacted]

Calculating PASI

In each area, the sum of the severity rating scores for erythema, induration and scaling is multiplied by the score representing the percentage of this area involved by psoriasis, multiplied by a weighting factor (head 0.1; upper limbs 0.2; trunk 0.3; lower limbs 0.4). The sum of the numbers obtained for each of the four body areas is the PASI.[1]

$$\text{PASI} = \begin{array}{l} 0.1Ah(Eh + Ih + Sh) + 0.2Au(Eu + Iu + Su) + \\ 0.3At(Et + It + St) + 0.4Al(El + Il + Sl) \end{array}$$

where A = area of involvement 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.

7.4.2. 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

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

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

CCI

[redacted]

CCI [redacted]

7.4.6. Target Lesion and Regional Photography (Psoriasis subjects only)

Standardized digital photographs of target lesions and surrounding region photography will be taken at selected study sites using a professional quality digital camera. These photographs are for illustrative purposes only.

Target Lesion Photography: Two target lesions will be selected at the Day -1 visit. Anything extraneous to each lesion and its surrounding area are to be removed from the photographic field. The camera/lens will be set at the appropriate magnification. A close-up attachment scale attached to the camera system will help ensure that photographs are all taken at the same magnification and from the same set distance. Photographs will be taken in duplicate with lighting, framing, and exposure held constant.

Regional Photography: Regional photographs of each target lesion and surrounding area will also be taken. Once the camera/lens is set at the appropriate magnification, proper focusing technique will help ensure that photographs are all taken from the same set distance from the camera. Photographs will be taken in duplicate with lighting, framing, and exposure held constant.

Digital study images will be captured on memory cards. The contents of those cards will be uploaded to Canfield Scientific, Inc. using Canfield's secure, compliant website. All study images received will be monitored and archived in a fully validated, 21 Code of Federal Regulations (CFR) Part 11 Food and Drug Administration (FDA) compliant system. A copy of each subject's Day -1 photographs will be provided to the investigational sites for the subject file in order to confirm the location/field of view to be photographed at the end of treatment. Photography will be performed at Day -1, Day 7, Day 14, and Day 28, as well as at the follow-up visits occurring at Day 42 and Day 56/Early Termination and Day 84. Additional instructions related to target lesion and Regional Photography can be located in the study manual.

CCI [redacted]

CCI [redacted]

7.6. Pharmacokinetics

7.6.1. Plasma for Analysis of PF-06826647

During all study periods, blood samples (4 mL) to provide approximately 1.2-1.5 mL plasma for pharmacokinetic analysis will be collected into appropriately labeled tubes containing K_2 EDTA at times specified in the Schedule of Activities section of the protocol.

The actual times may change but the number of samples will remain the same. All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF/DCT).

- Samples will be centrifuged at approximately 1700 x g for about 10 minutes at 4°C. The plasma will be stored in appropriately labeled screw capped polypropylene tube at approximately -20°C within 1 hour of collection.
    - Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.
    - Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the lab manual.
    - The PK samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the PK processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.
    - CCI [redacted]

7.6.2. Urine for Analysis of PF-06826647

Urine will be collected as outlined in the Schedule of Activities.

Urine will be stored at approximately 4°C during each collection period. At the end of each 24 hour urine collection period, the urine will be mixed thoroughly and total volume will be measured and recorded. A 7-8 mL aliquot will be withdrawn for measurement of drug concentrations and will be stored frozen at approximately -20°C within 1 hour of the end of the collection interval. The urine blank for PK will be obtained from the 24-hour collection on Day -1 (0-24 hr) for subjects undergoing QD or BID dosing. On Day 10, urine will be collected for the BID cohort over 2 time intervals: 0-12 and 12-24 hours. The Day 10 PK sample will be obtained from the 0-12 hour urine time interval during the potential BID cohort.

The PK samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the PK processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

The preferred tubes for collection and storage will be identified and this information will be provided to the site prior to start of the study. Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

As part of understanding the pharmacokinetics of the study drug, samples may be used for CCI identification and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical report.

7.6.3. Shipment of Pharmacokinetic Samples

The shipment address and assay lab contact information will be provided to the investigator site prior to initiation of the study.

CCI

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

CCI [redacted]

[redacted]

7.10. Blood Volume

The total blood sampling volume for individual subjects in this study is approximately 552.8 mL for the SAD and MAD cohorts and approximately 475 mL for the Psoriasis cohort. The actual collection times of blood sampling may change, but the total blood volume collected will not increase. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 30 consecutive days.

Table 8. Blood Volume: Single Ascending Dose Period

Sample Type	Sample Volume (mL)	Number of Sampling Times			
		Screening	Treatment Period	Follow-up Period	Total Volume (mL)
Interferon Gamma Release Assay (IGRA)	3	1	0	0	3
HIV, HepBsAg, HepBcAg, HCVAb	8.5	1	0	0	8.5
FSH	2	1	0	0	2
Blood Safety Labs (hematology & chemistry)	14.5	1	3	1	72.5
Fibrinogen	2.7	0	1	1	5.4
Lipid Panel	0	1	2	1	0
[redacted]	C CI	[redacted]	[redacted]	[redacted]	[redacted]
PK Blood Sampling	4	0	12	1	52
[redacted]	C CI	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL					**183.9**

Table 9. Blood Volume: Multiple Ascending Dose Period

Sample Type	Sample Volume (mL)	Number of Sampling Times			
		Screening	Treatment Period	Follow-up Period	Total Volume (mL)
Blood Safety Labs (hematology & chemistry)	14.5	0	7	1	116
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fibrinogen	2.7	0	2	0	5.4
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lipid Panel	0	0	4	1	0
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PK Blood Sampling	4	0	24	1	100
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL					**368.9**

Table 10. Blood Volume: Psoriasis Multiple Dose Period

Sample Type	Sample Volume (mL)	Number of Sampling Times			
		Screening	Treatment Period	Follow-up Period	Total Volume (mL)
Interferon Gamma Release Assay (IGRA)	3	1	0	0	3
HIV, HepBsAg, HepBcAg, HCVAb	8.5	1	0	0	8.5
FSH	2	1	0	0	2
Blood Safety Labs (hematology & chemistry)	14.5	1	9	3	188.5
[redacted]	C	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	C	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	I	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lipid Panel	0	1	5	1	0
[redacted]	C CI	[redacted]	[redacted]	[redacted]	[redacted]
PK Blood Sampling	4	0	14	1	60
[redacted]	C CI	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL					**475.0**

Total volumes for the tables above do not include discarded blood from pre-draws used to remove fluid from flushed catheters, if applicable.

7.11. Assessment of Suicidal Ideation and Behavior

CCI [redacted]

[redacted]

[redacted]

CCI

[redacted]

[redacted]

[redacted]

7.11.2. Patient Health Questionnaire – 8 items (PHQ-8)

Patient health questionnaire – 8 items (Appendix 11) is a patient-report questionnaire consists of 8 items to assess subject depression level.

At Screening Visit, if PHQ-8 total score ≥15, the subject will not be included in the study.

7.11.3. Suicidal Behaviors Questionnaire-revised (SBQ-R)

Suicidal behaviors questionnaire- revised (Appendix 10) is a patient-report questionnaire consists of 4 items to assess suicidal ideation, suicide attempts, threat of suicidal behavior, and likelihood of suicidal behavior.

At Screening Visit, if SBQ-R total score ≥8, the subject will not be included in the study.

7.12. Triggered Requirements

7.12.1. Potential Cases of Acute Kidney Injury

Abnormal values in serum creatinine (SCr) concurrent with decline in eGFR that meet the criteria described below in the absence of other causes of kidney injury, are considered potential cases of acute kidney injury and should be considered important medical events. An increase of ≥0.3 mg/dL (or ≥26.5 μmol/L) in serum creatinine relative to subjects' own baseline measurement should trigger another assessment of SCr to confirm, within 24-hours from awareness.

If the second (repeat) result is still of ≥0.3 mg/dL (or ≥26.5 μmol/L) relative to subject baseline, assessment of serum Cystatin C (S Cystatin C) should be referenced. Based on these measurements, estimated GFR using serum creatinine (2009 CKD-EPI eGFR[7]) and serum cystatin C (2012 CKD-EPI eGFR[7]) will be determined and reviewed, preferably within 72 hours and not later than 96 hours from the confirmed (repeat) elevated serum creatinine result.

If an individual subject demonstrates CONCOMITANT sCr-based AND S Cystatin C-based eGFR decline of ≥30%compared to the subject's baseline eGFR, then the subject should not be further dosed and adequate, immediate, supportive measures including **immediate evaluation by a nephrologist (preferably within 24 hours) with appropriate management** and treatment as clinically indicated. Results should be repeated as indicated by the nephrologist or weekly at a minimum until the eGFR returns to baseline ±15% or the renal parameters are deemed to be stable by the nephrologist and/or PI.

If the subject cannot be seen by a nephrologist within 24 hours (as described above), then the subject should be sent to a local emergency room for evaluation and treatment as clinically indicated.

Subjects should return to the investigational site and be evaluated as soon as possible, **preferably within 24-48-hours** from awareness of the abnormal eGFR result. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to evaluating eGFR as calculated by SCr and S Cystatin C, laboratory tests should include: serum blood-urea-nitrogen, serum creatine kinase, serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, calcium), in addition to urinary dipstick, urine microscopic examination, and urinary indices. All cases confirmed on repeat testing as meeting the eGFR criteria for acute-kidney-injury, with no other cause(s) of laboratory abnormalities identified should be considered as potential cases of drug-induced kidney injury irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal SCr. If ≥2 healthy subjects in a given cohort are noted to have 2 *consecutive* decreases from baseline in eGFR of -≥30%, based on both sCr AND S Cystatin C, an assessment of whether the finding may be considered adverse drug reaction should be undertaken.

This requirement applies to all subjects, all cohorts.

7.13. Rater Qualifications

Investigators participating in this study should be experienced in the conduct of psoriasis clinical trials and have prior training and experience in the required protocol-specific psoriasis subject clinical evaluations. **The same rater should evaluate the same subject(s) whenever possible.**

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety 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) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this 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 subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. 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.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal/Early Termination section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject provides informed consent, which is obtained before the subject'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 subjects who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject 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.

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.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. 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. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

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.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or

- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

  Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are 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.

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. 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 subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects 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 lab 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 subject’s individual baseline values and underlying conditions. Subjects 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:

- Subjects 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 subjects 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 subject 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, 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, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. 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) 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 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.

8.4.2. Exposure to the Investigational Product 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.

8.4.2.1. Exposure During Pregnancy

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 subject or subject's partner becomes or is found to be pregnant during the subject'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 subject 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

pre-procedure 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 subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.2.2. 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.

8.4.2.3. 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 subject 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.

8.4.3. Medication Errors

Other 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

8.4.3.1. Medication Errors

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

Medication errors include:

- Medication errors involving subject 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 participating subject.

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 non-serious, 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**.

9. DATA ANALYSIS/STATISTICAL METHODS

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

9.1. Sample Size Determination

9.1.1. Healthy Subject Single Ascending and Multiple Dose

A sample size of 8 subjects in each SAD and MAD cohort (with 6 active and 2 placebo) with approximately 48 subjects (assuming 6 cohorts) and 24 subjects for optional cohorts MAD BID cohort, Cohort 7 and 8 is not based on any statistical considerations. Sample size for optional Japanese subject cohort is not based on any statistical considerations, and may enroll up to 8 subjects in order to support characterization of the PF-06826647 PK profile in Japanese subjects. The sample size was based on the clinical consideration to provide safety and tolerability information and pharmacological considerations and on the need to minimize exposure to healthy subjects at each dose level. No formal inferential statistics will be applied to the safety, pharmacodynamic or pharmacokinetic data.

9.1.2. Psoriasis Multiple Dose

A sample size of approximately 42 subjects total is planned for the two psoriasis cohort(s). Psoriasis subjects will be randomized in each Psoriasis cohort to receive either active PF-06826647 (or placebo) with a planned randomization ratio of 2:1 (PF-06826647:Placebo) for each cohort. The between-subject standard deviation of absolute PASI change from baseline to Day 28 (obtained from Sponsor data on file) is assumed to be 8. The true difference between PF-06826647 and placebo is assumed to -7.8 (derived from the meta-analysis of the Tofacitinib data). Based on these assumptions the sample size is calculated to be 14 subjects per arm to provide approximately 80.7% power. This calculation assumes a one-sided alpha of 5%. The initial estimate of the total number of completers for the psoriasis cohort will be 42 with 21 (14 active +7 placebo) in each cohort. Based on the results from the planned interim analysis (described below in Section 9.7) PF-06826647 dose level or regimen may be adjusted for subsequent psoriasis subjects/cohorts enrolled after the interim analysis.

9.2. Efficacy Analysis

All subjects who receive at least one dose of randomized study medication, and have a baseline and at least one post-baseline measurement (after taking randomized study medication) will be included in the efficacy data analyses for the psoriasis cohorts.

9.2.1. Analysis of Secondary Endpoints

The change from baseline in PASI score at Day 28 in the psoriasis multiple dose segment is a secondary endpoint. The treatment effect for each of the test dose groups is the treatment difference in the mean change from baseline of PASI score at Day 28 between the test dose and the placebo. The estimates for treatment effect will be obtained by fitting a repeated measures linear model to the PASI change from baseline score. The model will include treatment (active doses and placebo), week and treatment-by-week interaction as fixed effects and baseline PASI score as a covariate. Estimates and 90% confidence intervals for treatment effect will be presented.

9.3. Pharmacokinetic Analysis

9.3.1. Single and Multiple Dose Periods

The PK data set will include data from all subjects receiving active drug and having any measurable concentration of study drug. Complete details will be provided in the study's SAP.

The following PK parameters will be calculated for PF-06826647 (if possible) from the plasma concentration-time data using standard noncompartmental methods:

Matrix	Parameter	Definition	Method of Determination
Plasma	AUC_{last}	Concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
	$AUC\tau$	Area under the plasma concentration-time profile over the dosing interval τ	Linear/Log trapezoidal method
	AUC_{inf} [a]	Area under the plasma concentration-time profile from time zero extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where Clast* is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis
	C_{max}	Maximum plasma concentration	Observed directly from data
	C_{min}	Lowest concentration observed during dosing interval, τ; if measured at end of dosing interval, equivalent to C_{trough}	Observed directly from data
	C_{av}	Average concentration at steady state	$C_{av}= AUC\tau,ss/\tau$
	T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
	$t_{1/2}$ [a]	Terminal elimination half-life	$Log_e(2)/k_{el}$, where kel is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression
	CL/F[a]	Apparent clearance	$Dose/AUC_{inf}$ for SD $Dose/AUC\tau$ for MD
	V_z/F[a]	Apparent volume of distribution	$Dose/(AUC_{inf}. k_{el})$ for SD $Dose/(AUC\tau. k_{el})$ for MD
	Rac	Observed accumulation ratio based on AUC	$AUC\tau$ (ss)/$AUC\tau$ (sd)
	$Rac,_{Cmax}$	Observed accumulation ratio based on C_{max}	C_{max} (ss)/ C_{max} (sd)
	PTR	Peak to Trough ratio	$C_{max},ss/C_{min},ss$
	MRT	Mean residence time	$AUMC_{inf}/AUC_{inf}$, where $AUMC_{inf}$ is the area under the first moment curve from time zero to infinity.
	C_{max}(dn)	Dose normalized C_{max}	C_{max}/Dose

Matrix	Parameter	Definition	Method of Determination
	AUC_{last}(dn)	Dose normalized AUC_{last}	AUC_{last}/Dose
	AUC_{inf}(dn)[a]	Dose normalized AUC_{inf}	AUC_{inf}/Dose
Urine	Ae_{τ}	Cumulative amount of drug recovered unchanged in urine from 0 to dose interval (τ) hours postdose	Sum of [urine concentration * sample volume] for each collection interval
	Ae_{τ}%	Percent of dose recovered unchanged in urine from 0 to dose interval (τ) hours postdose	Aeτ/Dose*100
	CLr	Renal clearance	Ae_{τ}/AUC_{τ}

[a] If data permit

The PK parameters will be summarized descriptively by dose, regimen and study population (healthy subject and psoriasis subject) in accordance with Pfizer data standards. Summary statistics will also include the geometric mean and coefficient of variation for all parameters except T_{max}.

Dose normalized (to 1 mg) AUC and C_{max} values of PF-06826647 will be plotted against dose (using a logarithmic scale if dose range is greater than 10-fold) for single- and multiple dose phases, and will include individual subject values and the geometric means for each dose. These plots will be used to help understand the relationship between the plasma PK parameters and dose. Additional PK analyses may be performed if deemed appropriate.

Urine amounts of PF-06826647 and CLr will be listed and summarized descriptively, if data permits.

CCI [redacted] Natural log transformed AUC_{24} and C_{max} will be analyzed using a mixed effect model with treatment (Dose levels) and period as a fixed effect and subjects within a treatment as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios. Further details will be provided in statistical analysis plan (SAP).

CCI [redacted]

[redacted]

CCI [redacted]

9.6. Safety Analysis – Primary

Adverse events, ECGs, blood pressure, pulse rate, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. Any clinical laboratory, ECG, BP, and PR abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination and neurologic examination information and continuous cardiac monitoring collected during the course of the study will not be captured for inclusion into the study database, unless otherwise noted. However, any untoward findings identified on physical and/or neurologic examinations or on telemetry monitoring conducted after the administration of the first dose of study medication will be captured as an adverse event, if those findings meet the definition of an adverse event. Data collected at Screening that is used for inclusion/exclusion criteria, such as laboratory data, ECGs and vital signs will be considered source data, and will not be captured for inclusion into the study database, unless otherwise noted. Demographic data collected at Screening will be included in the study database.

Data relevant to the assessment of suicidality will be mapped to the Columbia-Classification Algorithm of Suicide Assessment (C-CASA) codes. Baseline and post-baseline CCI data (mapped to C-CASA scores) will be summarized descriptively by treatment group at baseline and each post-baseline visit. The safety analyses will be carried out in the safety population, detailed analyses will be described in the SAP.

9.6.1. Electrocardiogram Analysis

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

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

Safety QTc

	Borderline (msec)	Prolonged (msec)
Absolute Value	≥450 - <480	≥480
Absolute Change	30-<60	≥60

In addition, the number of subjects with corrected and uncorrected QT values ≥500 msec will be summarized.

If more than one ECG is collected at a nominal time post dose (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. If any of the three individual ECG tracings has a QTc value ≥500 msec, but the mean of the triplicates is not ≥500 msec, the data from the subject's individual tracing will be described in a safety section of the study report in order to place the ≥500 msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are ≥500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also ≥500 msec. Changes from baseline will be defined as the change between QTc post dose from the average of the pre-dose triplicate values on Day 1.

In addition, an attempt will be made to explore and characterize the relationship between plasma concentration and QT interval length using a PK/PD modeling approach. If a PK/PD relationship is found, the impact of subject factors (covariates) on the relationship may be examined.

9.7. Interim Analysis

An interim analysis of the change from baseline at Day 28 in PASI score (psoriasis key secondary endpoint) will be conducted for the first psoriasis cohort (400 mg dose cohort). The analysis will be performed when 21 psoriasis subjects from the 400 mg cohort complete through study Day 28. Outcomes from this interim analysis may inform dose selection decisions/adjustments for later psoriasis subject cohorts to be enrolled in the study. The interim analysis is not planned to impact the conduct of the initial 400 mg psoriasis cohort. The analysis is planned to be performed after dosing of the full 400 mg psoriasis cohort

(n=21 subjects completing through study Day 28). Any decisions or dose adjustments that are taken, will be applied to the subsequent psoriasis cohort. A designated limited number of Sponsor colleagues will review the interim analysis results to support any dose related decisions. For the healthy SAD/MAD cohorts, this is a sponsor-open study, and the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating PK/PD modeling, and/or to support clinical development. Unblinded results will be reviewed by a designated limited number of sponsor colleagues within the study team.

The psoriasis multiple dose cohorts are double-blind with respect to investigator and subject. The psoriasis multiple dose cohorts will be sponsor-open (unblinded interim analysis results will be reviewed by a designated limited number of sponsor colleagues). In addition to the planned interim analysis from the 400 mg psoriasis cohort, the sponsor may analyze selected clinical endpoints at the end of the Psoriais treatment period (Day 28) before the follow-up period is completed for all cohorts. For the purpose of safety assessment, select individuals from sponsor may conduct unblinded reviews of individual subject safety data if needed to ensure proper management of subject safety. If needed, a designated limited number of sponsor colleagues may conduct unblinded reviews of the data during the course of the study to facilitate PK/PD modeling.

Refer to the study's Data Blinding Plan and/or Statistical Analysis Plan for specific details including delineation of study team members who will be involved in these unblinded reviews as well as steps to be instituted ahead of initiation of any unblinded review to ensure study integrity is maintained.

9.8. Data Monitoring Committee

This study will not use an external data monitoring committee (DMC).

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct for studies conducted at non-Pfizer investigator sites, to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs[/DCTs] are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer 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 subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

For studies conducted at non-Pfizer investigator sites, 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.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Data Collection Tools/Electronic Data Record

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 subject. 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's chart. In these cases, data collected on the CRFs must match 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.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent[/assent] documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent[/assent] documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by laws.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject’s numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects’ personal data consistent with applicable privacy laws.

The informed consent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. 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, Pfizer should be informed immediately.

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in the United States

Last subject last visit (LSLV) is defined as the date the investigator reviews the last subject's final safety data and determines that no further evaluation is required for the subject to complete the trial.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06826647 at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

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 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 Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are 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 subject 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 patients 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.

15.2. Publications by Investigators

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, subject 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 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 subjects, and the CSA will control as to all other issues.

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Appendix 1. Abbreviations

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

Abbreviation	Term
AE	adverse event
Abs	Absolute
$Ae_{12/24}$	amount of unchanged drug excreted into urine from time 0 to 12 hours or 0-24 hours, respectively
$Ae_{12/24}$%	percentage of dose excreted unchanged into urine from 0 to 12 hours or 0 to 24 hours, respectively
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
AUC_{0-24}	area under the concentration time curve from time zero to 24 hours after single dose
AUC_{24}	area under the concentration-time curve from time 0 to 24 hours
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
AUC_{last}	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
AUC_{tau}	area under the concentration-time curve over the the dosing interval tau
BA	Bioavailability
BBS	Biospecimen Banking System
BCG	bacille Calmette-Guérin
BE	Bioequivalence
BID	Bis in die (twice a day)
BMI	body mass index
BP	blood pressure
BPM	beats per minute
CCI	[redacted]
BU	business unit
BUN	blood urea nitrogen
C_{av}	average concentration
C-CASA	Columbia-Classification Algorithm of Suicide Assessment
CD	Crohn's disease
CDS	core data sheet

Abbreviation	Term
C_{eff}	efficacious concentration
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CI	confidence interval
CK	creatine kinase
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	plasma clearance
CL/F	Apparent total clearance of the drug from plasma after oral administration
CL_r	renal clearance
C_{max}	peak or maximum observed concentration
C_{min}	Minimum plasma drug concentration
CCI	[redacted]
CO_2	carbon dioxide (bicarbonate)
CRF	case report form
CRP	C-reactive protein
CRU	Clinical Research Unit
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSR	clinical study report
CCI	[redacted]
CT	clinical trial
CTA	clinical trial application
CTC	Common Terminology Criteria
DAI	dosage and administration instructions
DCT	data collection tool
DDI	Drug-drug interaction
DILI	drug-induced liver injury
CCI	[redacted]
DMC	data monitoring committee
DNA	deoxyribonucleic acid
CCI	[redacted]
EC	ethics committee
ECG	Electrocardiogram
EDMC	external data monitoring committee
EDP	exposure during pregnancy
EDR	Extemporaneous Dispensing Record

Abbreviation	Term
EDTA	edetic acid (ethylenediaminetetraacetic acid)
eGFR	estimated glomerular filtration rate
EOT	end of treatment
EPO	erythropoietin
ET	early termination
EU	European Union
EIU	exposure in utero
ESoE	Early signal of efficacy
ERB	external review board
EudraCT	European Clinical Trials Database
CCI	[redacted]
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FFPE	formalin-fixed paraffin-embedded
FIH	first in human
FISH	Fluorescence in situ hybridization
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GLDH	glutamate dehydrogenase
GLP	Good laboratory practice
GM-CSF	Granulocyte-Macrophage Colony Stimulating Factor
GBP1	Guanylate binding protein 1
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCT	Hematocrit
HCV	Hepatitis C virus
HCVAb	hepatitis C antibody
HDL-C	high density lipoprotein cholesterol
HED	human equivalent dose
HEP	human hepatocytes
HepBcAb	hepatitis B core antibody
HepBsAg	hepatitis B surface antigen
hERG	human ether a-go-go gene
HGB	hemoglobin

Abbreviation	Term
HIV	human immunodeficiency virus
HLM	human liver microsomes
CCI [redacted]	[redacted]
HSV	herpes simplex virus
CCI [redacted]	[redacted]
HVs	healthy volunteers
HWB	Human whole blood
IB	investigator's brochure
ICH	International Conference on Harmonisation
IC50	50% inhibitory concentration
ID	Identification
IEC	independent ethics committee
IFN	type I interferon
CCI [redacted]	[redacted]
IGRA	interferon gamma release assay
IND	investigational new drug application
INR	international normalized ratio
IL	interleukin
IOBU-SDMC	Internal Oncology Business Unit -Safety Data Monitoring Committee
IP	Investigational product
IR	Immediate release
IRB	institutional review board
IRC	internal review committee
CCI [redacted]	[redacted]
IUD	intrauterine device
IUS	Intrauterine system
IV	intravenous
JAK	Janus kinase
KDIGO	Kidney Disease: Improving Global Outcomes
KDR	kinase insert domain receptor
K_2EDTA	dipotassium ethylene diamine tetraacetic acid
LDLC	low density lipoprotein cholesterol
LFT	liver function test
LLN	lower limit of normal
L-PASI	Linear method Psoriasis Area and Severity Index
LPD	local product document

Abbreviation	Term
LSLV	last subject last visit
MAD	multiple ascending dose
MATE	multidrug and toxin extrusion protein
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDR1	multidrug resistant protein 1
MedDRA	medical Dictionary for Regulatory Activities
mRNA	messenger riboneuclic acid
MTD	maximum tolerated dose
MRP	multidrug resistance-associated protein
MRT	mean residence time
NAPAC	Neuropsychiatric and Abuse Potential Advisory Council
N/A	not applicable
NK	Natural Killer cell
CCI	[redacted]
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NRS	Numeric Rating Scale
NTCP	sodium/taurocholate co-transporting polypeptide
OATP	organic anion transporting polypeptide
OBU	Oncology Business Unit
OCT	organic cation transporter
OEB5	occupational exposure banding 5
CCI	[redacted]
PBMC	periperhal blood mononucleated cell
PCD	primary completion date
PCRU	Pfizer Clinical Research Unit
PD	Pharmacodynamics
PGx	Pharmacogenomics
P-gp	P glycoprotein
PHQ-8	Patient health questionnaire
PI	principal investigator
PK	Pharmacokinetics
PR	pulse rate
PROs	patient reported outcomes
PT	prothrombin time
CCI	[redacted]
PUVA	Psoralen ultraviolet A
QC	quality control
QD	Once daily
QFT	QuantiFERONR TB
QFT-G	QuantiFERONR TB Gold

Abbreviation	Term
QFT-GIT	QuantiFERON TB Gold In Tube test
QTc	corrected QT
RBC	red blood cell
RNA	ribonucleic acid
RSAD2	radical S-adenosyl methionine domain-containing protein 2
S Cystatin C	serum Cystatin C
SAD	ascending dose period
SAE	serious adverse event
SAP	statistical analysis plan
SBQ-R	Suicidal behaviors questionnaire
SCr	serum creatinine
sd	single dose
SDD	sprayed-dried dispersion
SGOT	serum glutamic oxaloacetic transminase
SGPT	serum glutamic pyruvic transminase
SIB	suicidal ideation and behavior
SLE	Systemic lupus erythematosus
SOP	standard operating procedure
SRSD	single reference study document
ss	steady state
STAT	Signal Transducer and Activator of Transcription
$T_{1/2}$	terminal half life
Tau	dosing interval of 12 or 24 hours
TB	tuberculosis
TBili	total bilirubin
TC	Total cholesterol
TG	Total triglycerides
Th1	T-helper 1
Th17	T-helper 17
Tmax	time to reach maximum concentration
THC	Tetrahydrocannabinol
CCI	[redacted]
CCI	[redacted]
UGT	UDP-glucuronosyltransferase
ULN	upper limit of normal
US	United States
USP18	ubiquitin specific peptidase 18
USPI	United States package insert
UV	ultraviolet
UVA	ultraviolet A
UVB	ultraviolet B
VEGFR2	vascular endothelial growth factor receptor 2
Vss	Apparent volume of distribution at steady state

Abbreviation	Term
V_Z/F	apparent oral volume of distribution
CCI	[redacted]
WBC	white blood cell

Appendix 2. Cockcroft-Gault Calculation

The Cockcroft-Gault formula may be used to calculate an Estimated Creatinine Clearance, which in turn estimates Glomerular filtration rate (GFR)

$$\text{Est. Creatinine Clearance (mL/min)} = \frac{([140-\text{Age(years)}] \times \text{Weight(kg)} \times \text{Factor}^{a})}{(72 \times \text{Serum Creatinine [mg/dL]})}$$

[a] Factor is equal to 0.85 in females, and 1.00 in males

Appendix 3. Prohibited Concomitant Medications

CYP1A2, CYP3A4, CYP2D6 Inhibitors	**CYP1A2, CYP3A4, Inducers**	**MATE substrates**
CYP 1A2	*CYP 1A2*	
Ciprofloxacin	Phenytoin	Dofetilide
Clinafloxacin	Rifampin	Metformin
Enoxacin	Ritonavir	
Fluvoxamine	Teriflunomide	
Oltipraz		
Rofecoxib		
Zafirlukast		
Etintidine		
Idrocilamide		
Methoxsalen		
Mexiletine		
Oral contraceptive		
Phenylpropanolamine		
Pipemidic acid		
Propafenone		
Propranolol		
Troleandomycin		
Vemurafenib		
CYP 2D6		
Quinidine		
Fluoxetine		
Dacomitinib		
Paroxetine		
Buproprion		
Cinacalcet		
Terbinafine		
Tipranavir		
Moclobemide		
Rolapitant		
Mirabegron		
Duloxetine		
Eliglustat		
Dronedarone		
CYP3A4	*CYP3A4*	
Viekira pak	Rifampin	
Indinavir	Mitotane	
Tipranavir	Avasimibe	

CYP1A2, CYP3A4, CYP2D6 Inhibitors	**CYP1A2, CYP3A4, Inducers**	**MATE substrates**
Ritonavir	Phenytoin	
Cobicistat	Carbamazepine	
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	Modafanil	
Conivaptan	Etravirine	
Nefazodone	Lersivirine	
Nelfinavir		
Saquinavir		
Idelalisib		
Boceprevir		
Erythromycin		
Fluconazole		
Atazanavir		
Darunavir		
Diltiazem		
Dronedarone		
Crizotinib		
Aprepitant		
Casopitant		
Amprenavir		
Faldaprevir		
Imatinib		
Verapamil		
Netupitant		
Nilotinib		
Tofisopam		
Cyclosporine		
Ciprofloxacin		
Isavuconazole		
Cimetidine		

Appendix 4. Estimated Glomerular Filtration Rate

The estimated GFR (eGFR) will be calculated using the 2 sets of equations developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), which utilize serum creatinine (SCr) and serum Cystatin C (S Cystatin C) respectively.[7]

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

If female and 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)

$CKD\text{-}EPI_{2012cys}$

If female and Scys is ≤0.8 mg/L:

- GFR (mL/min/1.73 m^2) = 133 x $(Scys/0.8)^{-0.499}$ x 0.996^{age} x 0.932

If female and Scys is >0.8 mg/L:

- GFR (mL/min/1.73 m^2) = 133 x $(Scys/0.8)^{-1.328}$ x 0.996^{age} x 0.932

If male and Scys is ≤0.8 mg/L:

- GFR (mL/min/1.73 m^2) = 133 x $(Scys/0.8)^{-0.499}$ x 0.996^{age}

If male and Scys is >0.8 mg/L:

- GFR (mL/min/1.73 m^2) = 133 x $(Scys/0.8)^{-1.328}$ x 0.996^{age}

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

Appendix 8. Patient Global Assessment of Psoriasis

Overall, how would you describe your psoriasis right now?

Choose only ONE response.

My psoriasis is:
- ☐ Severe
- ☐ Moderate
- ☐ Mild
- ☐ Almost Clear
- ☐ Clear (no psoriasis)

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

Appendix 10. Suicidal Behaviors Questionnaire-Revised (SBQ-R)

SBQ-R Suicide Behaviors Questionnaire-Revised

Patient Name _____ Date of Visit _____

Instructions: Please check the number beside the statement or phrase that best applies to you.

1. Have you ever thought about or attempted to kill yourself? (check one only)

- ☐ 1. Never
- ☐ 2. It was just a brief passing thought
- ☐ 3a. I have had a plan at least once to kill myself but did not try to do it
- ☐ 3b. I have had a plan at least once to kill myself and really wanted to die
- ☐ 4a. I have attempted to kill myself, but did not want to die
- ☐ 4b. I have attempted to kill myself, and really hoped to die

2. How often have you thought about killing yourself in the past year? (check one only)

- ☐ 1. Never
- ☐ 2. Rarely (1 time)
- ☐ 3. Sometimes (2 times)
- ☐ 4. Often (3-4 times)
- ☐ 5. Very Often (5 or more times)

3. Have you ever told someone that you were going to commit suicide, or that you might do it? (check one only)

- ☐ 1. No
- ☐ 2a. Yes, at one time, but did not really want to die
- ☐ 2b. Yes, at one time, and really wanted to die
- ☐ 3a. Yes, more than once, but did not want to do it
- ☐ 3b. Yes, more than once, and really wanted to do it

4. How likely is it that you will attempt suicide someday? (check one only)

- ☐ 0. Never
- ☐ 1. No chance at all
- ☐ 2. Rather unlikely
- ☐ 3. Unlikely
- ☐ 4. Likely
- ☐ 5. Rather likely
- ☐ 6. Very likely

Appendix 11. Patient Health Questionnaire – 8 items (PHQ-8)

PHQ-8

Over the last 2 weeks, how often have you been bothered by any of the following problems? (Use "✓" to indicate your answer)	**Not at all**	**Several days**	**More than half the days**	**Nearly every day**
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down	0	1	2	3
7. Troubleconcentratingonthings,suchas reading thenewspaperorwatchingtelevision.	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3

(For office coding: Total Score _____ = ___ + ___ + ___)