CLINICAL PROTOCOL

A PHASE 2A, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE SAFETY AND EFFICACY OF PF-06700841 IN SUBJECTS WITH MODERATE TO SEVERE PLAQUE PSORIASIS

Investigational Product Number:	PF-06700841
Investigational Product Name:	Tyk2/Jak1
United States (US) Investigational New Drug (IND) Number:	131067
European Clinical Trials Database (EudraCT) Number:	2016-004049-96
Protocol Number:	B7931004
Phase:	2a

[redacted]

[redacted]

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 1	17 January 2017	Protocol title page – added the European Clinical Trials Database (EudraCT) Number. Schedule of activities footnote: clarified that blood pressure and other vital signs are to be collected with the subject in the sitting position. Schedule of activities: added an electrocardiogram (ECG) assessment at study Day 1, pre-dose. This addition was made to ensure a baseline ECG is collected just prior to initial study administration. Decreased the resting time required prior to vital sign and ECG collection, from 10 minutes to 5 minutes of rest. Section 4.2: Added psoriasis medications Secukinumab (Cosentyx), and Ixekizumab (Taltz) as exclusionary and prohibited during the study. Added Apremilast (Otezla) as exclusionary if taken within 3 months of first dose of study drug, and prohibited during the study. Section 7.1.1 - added reticulocytes as part of the hematology laboratory panel. Implemented minor clarifications previously described in protocol administrative letters dated 26 Oct 2016 and 3 Nov 2016. Appendix 4, Prohibited Concomitant Medications: are P-gp (MDRI) substrates (eg, digoxin), P-gp inhibitor eg, quinidine or OCT2/ MATE substrate (eg, dofetilide). Subjects receiving drugs with narrow therapeutic index that are P-gp (MDRI) substrates (eg, digoxin) and drugs that are substrates of OCT2/ MATE (eg, dofetilide) and potent inhibitors of P-gp eg, quinidine are excluded from participation in the study to limit any potential interactions with the investigational product. CCI [redacted]

[redacted]

		CCI [redacted]
Original protocol	29 August 2016	Not applicable (N/A)

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

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PROTOCOL SUMMARY

Background and Rationale

PF-06700841 is a dual TYK2/JAK1 inhibitor with good selectivity profile over other human kinases. Based on its cytokine inhibition profile, PF-06700841 is expected to target the TH17 pathway directly by inhibiting TYK2 and indirectly by inhibiting JAK1, and to provide therapeutic benefit in the treatment of plaque psoriasis. In a first in human clinical trial of PF-06700841, psoriasis subjects who received active treatment with PF-06700841 once daily for 28 days had clinically meaningful decreases in disease activity. Preliminary safety and pharmacodynamic results from that trial support further development of PF-06700841 in plaque psoriasis.

This multicenter study is being conducted to provide additional PF-06700841 safety and tolerability data, and to further explore the clinical efficacy of PF-06700841 in the treatment of moderate to severe plaque psoriasis. Additionally, the study is intended to enable selection of oral dose and dosing regimen for the future clinical development of PF-06700841.

Objectives:

Primary Objective

- To evaluate the efficacy of PF-06700841 in moderate to severe plaque psoriasis.

Secondary Objectives

- To explore the efficacy of PF-06700841 induction and maintenance dosing regimens in moderate to severe plaque psoriasis.
- To assess the safety and tolerability of PF-06700841 induction and maintenance dosing regimens.

Endpoints:

Primary Endpoint

- Change from baseline in Psoriasis Area and Severity Index (PASI) score at Week 12.

Key Secondary Endpoint

- Proportion of subjects achieving a PASI 75 response at Week 12.

Other Secondary Endpoints

- Proportion of subjects achieving 50%, 75% and 90% reduction from baseline PASI at time-points specified in the study schedule of activities.

- Change from baseline in PASI scores at time-points specified in the study schedule of activities.
- Percent change from baseline in PASI scores at time-points specified in the study schedule of activities.
- Change from baseline in PASI score at Week 4.

Safety Endpoints

- Incidence and severity of adverse events, serious adverse events and withdrawals due to adverse events.
- Change from baseline in clinical laboratory values (chemistry, hematology, lipids).
- Change from baseline in vital signs.
- Change from baseline in electrocardiogram (ECG) parameters.

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Study Design:

This is a Phase 2, randomized, double-blind, placebo-controlled, parallel group, multicenter study in subjects with moderate to severe plaque psoriasis. During the first 4 week treatment period, 2 oral daily dose levels (30 mg and 60 mg) of PF-06700841, plus matching placebo, will be investigated. During the 8 week maintenance treatment period (Weeks 5 through 12), subjects will receive either 10 mg or 30 mg PF-06700841 once daily, or a 100 mg once weekly regimen of PF-06700841, or matching placebo. Maintenance dose level and regimen will be assigned at the initial time of randomization into the study. The duration of study subject participation will be approximately 26 weeks, including screening, 12 week treatment period, and 8 week follow up period.

Statistical Methods:

The analysis of the primary endpoint will be change from baseline in PASI score at Week 12, with treatment effect in each of the active treatment groups defined as the placebo adjusted change from baseline in PASI score at Week 12 (mean change from baseline at Week 12 in the active treatment group minus the mean change from baseline at Week 12 in the placebo group).

[redacted]

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 on the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Study Procedure	**Screening**	**Baseline**	**Induction Period**			**Maintenance Period**				**Follow-up Period**		
Visit Identifier	**Week -1 to -6**	**Week 0**	**Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12/ Early Termination[b]**	**Week 14**	**Week 16 / Early Termination[b]**	***Week 20 (telephone follow-up)**
Study Day[a]	**Day -42-0**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**
Visit Window (Days) based on Day 1 visit	**N/A**		**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**N/A**
Informed consent	X											
Medical history[c] and demography	X											
Complete physical examination[d]	X	X			X				X			
Targeted physical examination[d]			X	X		X	X	X				
Vital signs[e]	X	X	X	X	X	X	X	X	X			
12-Lead ECG[e]	X	X			X				X			
Current /Prior Medications	X											
Height[f]	X											
Weight[f]	X	X			X				X			
Chest radiograph[g]	X											
Contraception check	X	→	→	→	→	→	→	→	→	→	→	→
Eligibility assessment	X	X										
Randomization		X										
Telephone follow-up												*X
Laboratory Assessments												
Hematology	X	X	X	X	X	X	X	X	X	X	X	

Study Procedure	**Screening**	**Baseline**	**Induction Period**			**Maintenance Period**				**Follow-up Period**		
Visit Identifier	**Week -1 to -6**	**Week 0**	**Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12/ Early Termination[b]**	**Week 14**	**Week 16 / Early Termination[b]**	***Week 20 (telephone follow-up)**
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Visit Window (Days) based on Day 1 visit	**N/A**		**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**N/A**
**Blood chemistry (full panel 1)	X	X		X	X		X		X		X	
**Blood chemistry (limited panel 2)			X			X		X		X		
***Serum Cystatin-C		X							X			
Lipid Panel (fasting): total cholesterol, LDL, HDL, triglycerides		X		X	X		X		X		X	
Urinalysis[h]	X	X	X	X	X	X	X	X	X			
HBsAg, HBcAb, HCV Ab, HCV RNA PCR if HCV Ab positive[i]	X											
HIV serology[j]	X											
CCI		X		X	X				X			
CCI		X			X		X		X			
CCI		X			X		X		X			
FSH	X											
Serum β-HCG[m]	X											
Pregnancy Test[m]		X	X	X	X	X	X	X	X	X	X	
IGRA TB testing[n]	X											
Laboratory Pharmacodynamics												
CCI		X		X	X		X		X		X	
CCI		X	X	X	X		X		X	X	X	

Study Procedure	Screening	Baseline	Induction Period			Maintenance Period				Follow-up Period		
Visit Identifier	**Week -1 to -6**	**Week 0**	**Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12/ Early Termination[b]**	**Week 14**	**Week 16 / Early Termination[b]**	***Week 20 (telephone follow-up)**
Study Day[a]	**Day -42-0**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**
Visit Window (Days) based on Day 1 visit	**N/A**		**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**N/A**
CCI		X	X	X	X		X		X			
CCI		X										
CCI		X		X	X		X		X			
CCI		X		X	X		X		X			
CCI												
		X	X	X	X	X	X	X	X			
				X	X	X	X	X	X			
					X				X			
Study treatment												
Investigational product dispensing[q]		X	X	X	X	X	X	X				
Investigational product accountability[p]			X	X	X	X	X	X	X			
Subject dosing diary[p]			X	X	X	X	X	X	X			
Clinical Assessments												
Clinical Evaluation: PASI[r], BSA[r]	X	X	X	X	X	X	X	X	X	X	X	
Clinical Evaluation: PGA[r]		X	X	X	X	X	X	X	X	X	X	
CCI		X	X	X	X	X	X	X	X	X	X	
CCI		X		X	X		X		X		X	
CCI		X			X		X		X		X	
PHQ-8[t]	X											
SBQ-R[t]	X											

Study Procedure	**Screening**	**Baseline**	**Induction Period**			**Maintenance Period**				**Follow-up Period**		
Visit Identifier	**Week -1 to -6**	**Week 0**	**Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12/ Early Termination[b]**	**Week 14**	**Week 16 / Early Termination[b]**	***Week 20 (telephone follow-up)**
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Visit Window (Days) based on Day 1 visit	**N/A**		**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**N/A**
C-SSRS[t]	X	X			X		X		X			
Clinical Evaluation: Plaque Lesion Photography[u]		X			X				X		X	
Additional regular monitoring												
Concomitant Treatment(s)		X	→	→	→	→	→	→	→	→	→	→
Serious and non-serious adverse event monitoring	X	→	→	→	→	→	→	→	→	→	→	→

Abbreviations: →= ongoing/continuous event; ECG = electrocardiogram;

* Week 20 visit is conducted via telephone follow up. AE assessment will be conducted verbally over the phone and if needed subject will be asked to come in for AE assessment. Use of contraception will be confirmed over the phone with the subject. Concomitant treatments will be reviewed and collected if any new medications/treatments have been initiated since last visit.

** Full Serum Chemistry **Panel 1** consists of Blood Urea Nitrogen (BUN), Serum Creatinine, Glucose, Ca^{++}, Na^{+}, K^{+}, Cl^{-}, Total CO_2, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Total bilirubin, Alkaline phosphatase, Uric acid, Albumin, Total Protein, Lactic Dehydrogenase (LDH). **Subjects must be fasting (water only) for 8 hours prior to** visits on **Day 1, Weeks 2, 4, 8, 12, and 16**. Serum Chemistry **Panel 2** consists of serum hepatic function testing (AST, ALT, total bilirubin, albumin), and serum creatinine, blood urea nitrogen (BUN). Fasting is not required for visits where the limited chemistry panel 2 is collected.

***Serum Cystatin-C will be collected at baseline (Day 1, pre-dose) and end of treatment (Week 12/ET) for all subjects. A serum creatinine result above the upper limit of normal will trigger cystatin-C reflect testing in order to calculate estimated GFR. Refer to Section 7 for more details.

a. Day relative to start of study treatment (Day 1).
b. For subjects who discontinue early from the double-blind period prior to **Week 12** visit, the procedures scheduled for **Week 12** will be performed on the last day the subject takes the investigational product or as soon as possible thereafter. For subjects who discontinue early prior to the **Week 16** visit, the procedures scheduled for **Week 16** will be performed at the early termination visit.
c. Medical history includes detailed histories of conditions outlined in Section 7.1.7.
d. Complete physical examination consists of general appearance, skin, head, eyes, ears, nose and throat (HEENT), heart, lungs, breast (optional), abdomen, external genitalia (optional), extremities, neurologic function, back, and lymph nodes. Targeted physical examination consists of skin, heart, lungs, abdomen, and examination of body systems where there are symptom complaints by the subject.

e. Vital signs and ECG should be performed after the subject has rested quietly for at least 5 minutes and before laboratory blood collection. Vital signs consist of blood pressure, pulse rate, and temperature. Subjects should not smoke or ingest caffeine 30 minutes prior to blood pressure and pulse rate measurements. Sitting BP, pulse rate, and temperature will be measured at times specified in the Schedule of Activities.

f. Height and weight will be measured without shoes.

g. Chest X-ray or other appropriate diagnostic imaging (ie, CT or MRI) may be performed up to 12 weeks prior to Day 1. Official reading must be located in the source documentation.

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

i. Subjects who are HCV Ab positive require further testing with HCV RNA PCR. Subjects with false positive anti-HBc may be enrolled based upon consultation with hepatologist confirming no infection with hepatitis B.

j. If not performed within 12 weeks prior to screening. Copy of the report should be available in the source document if previously performed.

k. CCI [redacted]

l. To be done in females who are amenorrheic for at least 12 consecutive months.

m. Required for female subjects of childbearing potential that do not meet the definition of menopause as per the inclusion/exclusion criteria. Serum pregnancy test must be performed at screening. Pregnancy tests (serum/urine) may also be repeated more frequently as per request of IRBs/ECs or if required by local regulations. If serum pregnancy test is borderline positive, the central lab will run a FSH test to confirm menopause, assuming other menopause criteria are met per protocol eligibility requirements.

n. If not performed within 12 weeks prior to screening (see Assessments Section 7.1.4 for details). (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).

o. CCI [redacted]

p. Drug Accountability procedures are to be performed at Weeks 1, 2, 4, 6, 8, 10, 12, and at the Early Termination visit.

q. Subjects should take blinded study medication from study Days 1 to 85 during the trial; however, on study visit days, subjects are to be instructed to refrain from dosing at home, and are to take the morning dose in the clinic.

r. Psoriasis Area and Severity Index (PASI); Body Surface Area (BSA); Physician's Global Assessment (PGA); CCI [redacted] CCI [redacted]. CCI [redacted] are to be completed at clinic visits prior to other clinical assessments and administration of study medication.

s. CCI [redacted]

t. Subjects who have recent or active suicidal ideation or behavior will be excluded from the study per Section 4.2.

u. Target lesion and regional photography will be performed at selected study sites.

v. If not collected on the designated collection day, collect at the next available time point CCI [redacted] in conjunction with a subject visit.

[redacted]

1. INTRODUCTION

1.1. Mechanism of Action/Indication

PF-06700841 is a potent TYK2/JAK1 inhibitor with an excellent selectivity profile over the other human kinases. Thus, PF-06700841 is targeted for clinical development for the treatment of patients with psoriasis.

The most common variant of psoriasis, plaque psoriasis, is a chronic inflammatory skin disease characterized by red, scaly, raised plaques. In the past, psoriasis had been viewed as primarily a disease of epidermal hyperplasia, but more recently psoriasis has come to be regarded as an immune-mediated disease.[1] Cutaneous and systemic overexpression of T cells, as well as type-1 cytokines such as IL-2, IL-6, IL-8, IL-12, IL-23, IL- 17, have been implicated in the pathophysiology of chronic plaque psoriasis.[2] T-cell infiltration and associated pro-inflammatory cytokines drive epidermal hyperplasia characterized by increased cell division and aberrant differentiation that result in the psoriatic phenotype.[1,3,4] Chronic plaque psoriasis is a common skin disorder with a worldwide prevalence of 2% and afflicts an estimated 5.8-7.5 million Americans.[5] Although psoriasis primarily affects the skin and is not a life-threatening disease, it can profoundly impact the quality of life resulting in impairment akin to other major diseases such as type 2 diabetes, myocardial infarction, and arthritis.[6]

1.2. Background and Rationale

The Janus kinase (JAK) family, including JAK1, JAK2, JAK3 and TYK2, is a group of cytoplasmic tyrosine kinases that mediate signal transduction via interactions with Type 1 and Type 2 cytokine receptors critical for immune cell function, survival, activation, and proliferation.[7,8] 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.

JAK1-dependent cytokines include IFN-alpha, IFN-gamma, IL-6, IL-21, and IL-22. IL-6 and IL-21 play a critical role in the development of Th17 cells and production of IL-17, which is a target of several efficacious biologic therapies. JAK1-selective inhibitors spare dose-limiting effects of pan-JAK inhibition by preserving JAK2 homodimer signaling and thus provide the potential for more efficacious oral treatments for several inflammatory diseases including psoriasis. The previous positive psoriasis studies with two JAK1 selective inhibitors, INCB39110 and GSK2586184, have provided clinical support for JAK1 inhibition as a novel approach to treat plaque psoriasis.

Over activation of TH17 and the main effector cytokines of TH17 cells has been linked to various inflammatory diseases, including psoriasis.[9] TH17 cells are elevated in psoriatic lesions, along with levels of proinflammatory cytokines, including IL-17A, IL-17F, IL-17C, which are expressed by TH17 cells and are likely mediators of inflammation and tissue damage.[9,10] Human genetic studies implicate the TH17 pathway in psoriasis, and have uncovered likely risk alleles which include genes involved in IL-23 signaling and genes that function downstream of the IL-17 receptor.[9] In addition to genetic evidence, several effective psoriasis therapies target TH17 cytokine production, suggesting a central role of

TH17 and IL-17 in the disease. Secukinumab selectively targets IL-17A and has been shown to be effective in the treatment of psoriasis, and other therapies such as cyclosporine, phototherapy, and infliximab inhibit the TH17 pathway.[11,12,13,14] The monoclonal antibody Ustekinumab, disrupts IL-23 activation of TH17 cells by blocking the IL-23 receptor, and has proven to be effective in treating psoriasis.[15] Thus, there is strong rationale for targeting the TH17 pathway in the treatment of psoriasis.

PF-06700841 is a dual TYK2/JAK1 inhibitor with good selectivity profile over other human kinases. Based on its cytokine inhibition profile, PF-06700841 is expected to target the TH17 pathway directly by inhibiting TYK2 and indirectly by inhibiting JAK1, and to provide therapeutic benefit in the treatment of plaque psoriasis. In the first in human clinical trial of PF-06700841 (Study B7931001), psoriasis subjects receiving active treatment with PF-06700841 (30 mg or 100 mg once daily for 28 days) had clinically meaningful decreases in disease activity as measured by PASI. Preliminary safety, efficacy and pharmacodynamic results from Study B7931001 support further development of PF-06700841 in plaque psoriasis.

The current trial B7931004 is a Phase 2 study that will assess the safety and efficacy of several dose levels of PF-06700841, and will include daily and weekly dosing regimens in subjects with moderate to severe chronic plaque psoriasis.

1.3. Non-Clinical Pharmacokinetics and Metabolism

The pharmacokinetics (PK) of PF-06700841 have been studied in rat where the compound has shown a plasma clearance of 31 mL/min/kg, a volume of distribution of 2.0 L/kg, and oral bioavailability of approximately 80-100%. The high oral bioavailability indicated high absorption from the gut, consistent with its high in-vitro passive permeability properties. Rat in vivo clearance was predicted within approximately 2-fold by both in vitro rat liver microsomes and hepatocyte intrinsic clearance highlighting the importance of CYP450 metabolism. Systemic exposures of PF-06700841 as measured by C_{max} and area under the curve at 24 hours (AUC_{24}) in repeat oral pivotal toxicology studies increased with increasing dose in rats (up to 55 mg/kg/day) and monkeys (up to 45 mg/kg/day). Renal and biliary elimination of parent PF-06700841 was limited in rat.

Plasma protein binding of PF-06700841 was consistent across rat, monkey, and human with a fraction unbound (fu) of approximately 0.6-0.7. Values of fu were lower in mouse (fu = 0.51) and rabbit (fu = 0.36).

Oxidative metabolites of PF-06700841 accounted for the primary routes of biotransformation in rat, monkey, and human consistent with CYP450 as the primary clearance route. No unique human metabolites of PF-06700841 were evident compared to the safety species of rat and monkey.

Clearance phenotyping of PF-06700841 indicated that CYP3A4 will be the predominant mediator of human metabolism with minor contributions from CYP1A2, 2C19, and 2D6.

PF-06700841 showed a low risk of CYP450 inhibition and induction, uridine glucuronyl transferase (UGT) inhibition, OATP1B1/1B3 inhibition, and MDR1 inhibition. PF-06700841 showed some potential to inhibit metformin mediated transport by OCT2 (IC_{50}=1.1 μM), MATE1 (IC_{50}=7.7 μM) and MATE2K (IC_{50}=17 μM) in vitro. The respective unbound I_{max}/IC_{50} ratios are 0.65, 0.09, and 0.04 for a predicted 60 mg clinical dose of PF-06700841 (unbound C_{max}=0.72 μM). SimCYP modeling indicated a low risk of drug-drug interactions (DDI) perpetrated by a 60 mg once daily (QD) dose of PF-06700841 (C_{max}/AUC ratios 1.19/1.20).

1.4. Non-Clinical Safety Studies

PF-06700841 was evaluated in single-dose and repeat-dose toxicity studies up to 6 months (rats) and 9 months (monkeys) in duration. Dose range-finding and pivotal embryo-fetal development studies (EFD) were conducted with PF-06700841 in rats and rabbits. Target organs identified with PF-06700841 administration in rats and cynomolgus monkeys include the immune and hemolymphatic systems (thymus, spleen, lymph nodes, and bone marrow), gastrointestinal tract (body weight and weight gain effects), and adrenal gland (vacuolation). The findings in the thymus, spleen, lymph nodes, and bone marrow are consistent with the pharmacological activity of PF-06700841 and were not adverse because they were not associated with adverse clinical signs or adverse changes in hematology parameters, and there was no evidence of test article-related infections in these animals. Gastrointestinal and adrenal effects were not adverse because they were either transient, of small magnitude and/or severity, and/or lacked associated tissue injury or inflammation, or changes in clinical pathology parameters. In addition, there were inconsistent findings in the bone, liver, lung and prostate where the relationship to PF-06700841 is less clear. Adverse findings in the central nervous system (decreased activity, mortality, prostration, convulsions) were observed at high exposures in pregnant rabbits, and emesis was observed in monkeys at high doses in studies ≤1 month in duration. In safety pharmacology assessments PF-06700841-related effects were observed in the cardiovascular system (blood pressure, heart rate, QTc interval) and central nervous system (decreased locomotor activity). Based on the lack of adverse findings at any dose, the no observed adverse effect levels (NOAELs) in the 6-month rat and 9-month monkey studies were 45 mg/kg/day in rats and 20 mg/kg in cynomolgus monkeys. Exposures at these doses were 6.2x to 40x the predicted efficacious human exposure (C_{max}= 218 ng/mL and AUC_{24}= 1730 ng•h/mL) from a 50 mg dose.

In the pivotal EFD study in rats, there were no PF-06700841-related maternal effects. However, higher incidences of fetal skeletal malformations (in long bones, scapulae, sternebrae or palatine bones) and variations (in the ribs, cervical vertebrae or sternebrae) occurred at ≥2 mg/kg/day, and delays in the ossification of the axial and appendicular skeleton occurred at 15 mg/kg/day. In addition, lower embryo-fetal viability; lower mean fetal body weights, external malformations (cleft palate) and variations (whole body subcutaneous edema or edematous neck) occurred at 15 mg/kg/day. The maternal NOAEL in rats was 15 mg/kg/day (13x and 11x the predicted efficacious human C_{max} and AUC_{24} exposure from a 50 mg dose) and the developmental NOAEL was not determined but was <2 mg/kg/day, the lowest dose tested (2.2x and 1.3x the predicted efficacious human C_{max} and AUC_{24} exposure from a 50 mg dose). In the pivotal EFD study in rabbits, there were no

PF-06700841-related maternal effects. However, test article-related higher incidences of late resorptions and post-implantation loss occurred at ≥3 mg/kg/day and lower mean numbers of viable fetuses occurred at 7 mg/kg/day. Test article-related skeletal variations were observed at ≥3 mg/kg/day, but were not adverse because most of these findings represent delays in ossification that would resolve with further growth and development. The maternal NOAEL in rabbits was 7 mg/kg/day, the highest dose tested, (6.6x and 3.2x the predicted efficacious human C_{max} and AUC_{24} exposure from a 50 mg dose) and the developmental NOAEL was 1 mg/kg/day (0.8x and 0.4x the predicted efficacious human C_{max} and AUC_{24} exposure from a 50 mg dose).

PF-06700841 was negative for mutagenicity in the bacterial reverse mutation assays. Although PF-06700841 was positive in the in vitro micronucleus assays in both CHO and TK6 cells, and was aneugenic in vitro (at 72,100 nM), it did not induce micronuclei, in vivo, in reticulocytes in the 1-month study in rats (at exposures 35x to 51x the predicted human efficacious exposure (unbound C_{max} = 218 ng/mL and AUC_{24} = 1730 ng•h/mL) from a 50 mg dose.

Although PF-06700841 absorbs in the ultraviolet A (UVA) and ultraviolet B (UVB) range, PF-06700841 (≤100 mg/kg/day [unbound C_{max} and AUC_{24} were 46x and 82x the predicted efficacious human exposure from a 50 mg dose]) had no evidence of phototoxicity in the skin or eyes of pigmented Long Evans rats in a 3-day phototoxicity study. This demonstrates that PF-06700841 was not a phototoxicant, in vivo.

In summary, the nonclinical studies adequately support the planned clinical trials with PF-06700841.

Please refer to the Investigators Brochure for more details on the nonclinical information with PF-06700841.

1.5. Summary of Clinical Experience with PF-06700841

The B7931001 first in human study is the single clinical trial of PF-06700841 completed to date. Of the 96 subjects randomized, 74 subjects have received at least one active dose of oral PF-06700841 in Study B7931001. This accounts for 41 healthy subjects who participated in the single and multiple ascending dose period of the trial who received active solution/suspension, 12 healthy subjects from the bioavailability (BA) study who received suspension/tablet, and 21 subjects with chronic plaque psoriasis who were randomized to receive active solution/suspension over a 28 day treatment period.

The first in human (FIH) study was a Phase 1, randomized, double blind, third party open, placebo controlled, single and multiple dose escalation, parallel group study in healthy adult subjects and subjects with plaque psoriasis, with a relative bioavailability and food effect assessment of a tablet formulation of PF-06700841 in healthy adult subjects. During the single ascending dose (SAD) period, 41 healthy subjects received doses of 1, 3, 10, 30, 100, or 200 mg of PF-06700841 in a dose escalation format. Twenty-one healthy subjects received doses of 10, 30, 100, or 175 mg QD for 10 days during the multiple ascending dose (MAD) period. Subjects participating in the 100 mg multiple dose cohort returned for a third

period to receive 50 mg PF-06700841 BID for 10 days. Thirty subjects with moderate to severe chronic plaque psoriasis were also randomized into Study B7931001, to receive once daily placebo (n=9), 30 mg (n=14), or 100 mg (n=7) PF-06700841 for 28 days, and underwent safety monitoring and clinical efficacy assessments. An additional healthy volunteer cohort was included to support the evaluation of the relative bioavailability (BA) of a tablet formulation of PF-06700841, and assessment of a high fat meal on tablet bioavailability. 12 healthy subjects participated in this BA assessment, and received single doses of open label PF-06700841 in a 3-way cross over design (PF-0670841 tablet fasted, PF-06700841 solution/suspension fasted, and PF-06700841 tablet under fed conditions).

1.5.1. Summary of Clinical Safety Experience with PF-06700841

PF-06700841 was generally safe and well tolerated in the Phase 1 clinical study B7931001, which included both healthy subjects (n=66 randomized) and subjects with plaque psoriasis (n=30 randomized). There were no deaths in the study, no serious adverse events, and no severe adverse events. Subjects reported 11 treatment emergent adverse events TEAEs in the SAD phase, 22 TEAEs in the MAD phase, 39 TEAEs in the psoriasis phase, and 3 TEAEs in the BA phase. All adverse events (AEs) were mild or moderate in severity. Dose escalation stopping rules were not triggered at any dose level.

The most commonly reported all causality TEAEs across active subjects in both SAD and MAD cohorts were blood creatinine increased (reported in 2 subjects during the SAD period and 11 subjects during the MAD period), and neutropenia/neutrophil count decreased (reported in 4 subjects during the MAD period), which belong to the System Organ Class (SOC) categories of Investigations and Blood and Lymphatic System Disorders, respectively.

During the SAD/MAD, the AEs of blood creatinine increased were reported across dose levels from 10 mg up to 200 mg of PF-06700841, and occurred with greatest frequency in the 175 mg QD and 50 mg BID MAD cohorts. Common terminology criteria for adverse events (CTCAE) Grade 3 neutropenia occurred at the 175 mg QD and 50 mg BID dose levels during the MAD period. All laboratory abnormalities reported as AEs were mild in severity, except for one case of neutropenia which was reported as moderate in severity (Grade 3 neutropenia). No neutrophil counts reached, or fell below 500 cells/mm^3 during the study.

Other commonly reported all causality TEAEs during the SAD/MAD by SOC were Nervous System Disorders (2 events of headache and 1 event each of dizziness and presyncope during the SAD period, and 1 event each of headache, presyncope, and syncope reported during the MAD period), and Infections and Infestations (upper respiratory tract infection reported in 2 subjects during the MAD period). The AEs of upper respiratory tract infection were reported in 1 subject who received 10 mg PF-06700841 QD and 1 subject who received 100 mg PF-06700841 QD. These infections did not require antibiotic therapy (1 subject received symptomatic treatment), and did not require study treatment discontinuation.

The most commonly reported all causality TEAEs across active subjects in the psoriasis cohorts treated with either 30 mg or 100 mg PF-06700841 were blood creatinine increased (reported in 7 subjects in the 30 mg dose group and 6 subjects in the 100 mg dose group),

neutrophil count decreased (reported in 1 subject in the 30 mg dose group and 1 subject in the 100 mg dose group), which belong to the SOC category of Investigations.

Other commonly reported AEs by SOC in the psoriasis cohorts included Nervous System Disorders (headache reported in 1 subject in the 30 mg dose group and 1 subject in the 100 mg dose group, and paresthesia reported in 1 subject in the 100 mg dose group), Gastrointestinal Disorders (constipation reported in 3 subjects in the 30 mg dose group), and Infections and Infestations (1 report of upper respiratory tract infection and 1 report of herpes zoster infection, both in the 100 mg dose group).

The AE of herpes zoster occurred in a single subject after completing 28-day treatment with PF-06700841 at the 100 mg QD dose level. The subject had a non-disseminated, herpetiform rash on the upper left back and left arm that was reported to have presented on Study Day 30 (2 days after the last dose of PF-06700841). The AE was mild in severity and was treated with acyclovir and Vicodin by the Investigator.

In the BA cohort, the SOCs with subjects reporting AEs were Gastrointestinal Disorders, Injury, Poisoning, and Procedural Complications, and Nervous System Disorders, each reported by 1 subject. The reported AEs were nausea, contusion, and headache, each of which was experienced by 1 subject. Subjects in the PF-06700841 100 mg oral solution/suspension fasted group reported 1 treatment-related TEAE each of nausea and headache. All TEAEs were mild in severity.

Despite the AEs of blood creatinine increased observed in the healthy subjects (n=13 in the SAD/MAD cohorts) and psoriasis patients (n=13), review of clinical laboratory parameters from Study B7931001 confirmed there have been no noted clinically meaningful changes in the blood urea nitrogen, serum electrolytes, urinalysis, or cystatin-c based estimated glomerular filtration rate (eGFR) in the subjects with elevated serum creatinine. Serum creatinine is primarily filtered by the kidney however; approximately 10-20% is actively secreted into the renal proximal tubules. The active tubular secretion is mediated by transporters such as OCT2, OAT2 and MATEs. The proposed mechanism for the observed serum creatinine increases observed in Study B7931001 is inhibition of creatinine transport (ie, transporter-mediated rather than direct nephrotoxicity), and is based on PF-06700841 potential to inhibit OCT2 creatinine transporter (IC_{50}=1.1 μM; unbound I_{max}/IC_{50} ratio=0.25). To differentiate from direct nephrotoxicity, the B7931001 protocol was amended (Protocol Amendment 2) to include collection of serum cystatin C. Serum cystatin C was used to calculate eGFR in order to monitor for nephrotoxicity during the trial. Elevated serum creatinine in the absence of clinically meaningful changes in serum cystatin C based estimated GFR during Study B7931001 supports the transporter inhibition hypothesis. Following the implementation of cystatin C based safety monitoring, no subjects were discontinued from treatment/study due to renal concerns.

Proof of mechanism for JAK-1 inhibition was demonstrated in Study B7931001 by inhibition of pharmacodynamic (PD) biomarkers hs-CRP and IP-10. Safety data generated in Study B7931001 support PF-06700841's further clinical development in patients with moderate-severe plaque psoriasis.

Please refer to the Investigator Brochure (IB) for more details on the clinical safety information with PF-06700841.

1.5.2. Pharmacokinetics of PF-06700841

PK data from single doses of 1, 3, 10, 30, 100 and 200 mg and multiple doses of 10, 30, 100 and 175 mg QD and 50 mg BID mg administered for 10 days are summarized in Table 1 and Table 2, respectively. Following single oral doses of 1 mg to 200 mg under fasted conditions, PF-06700841 was absorbed rapidly with median T_{max} of 1 hour or less. Following the attainment of C_{max}, concentrations appeared to decline in monophasic fashion. Mean terminal $t_{½}$ ranged from 3.8 to 7.5 hours. In general, both AUC_{inf} and C_{max} appear to increase proportionally with dose from 1 mg to 100 mg, and there appears to be a trend toward more than proportional increases from 100 mg to 200 mg for AUC_{inf} and C_{max}.

Table 1. Summary of Plasma PF-06700841 Pharmacokinetic Parameters Following Single Oral Doses, Study B7931001

	PF-06700841 Parameter Summary Statistics[a] by Treatment					
Parameter, units	**1 mg**	**3 mg**	**10 mg**	**30 mg**	**100 mg**	**200 mg**
N, n	7, 2	6, 5	6, 6	6, 6	8, 7	8, 8
AUC_{inf}, ng.hr/mL	NR	145.8 (61)	353.8 (31)	1439 (65)	4797 (62)	18410 (46)
AUC_{last}, ng.hr/mL	17.71 (114)	79.18 (239)	340.4 (30)	1431 (65)	5041 (59)	18400 (46)
C_{max}, ng/mL	5.138 (52)	18.21 (92)	79.30 (35)	271.3 (21)	748.4 (35)	2460 (37)
T_{max}, hr	1.00 (0.500-2.00)	1.00 (0.500-1.00)	0.500 (0.500-1.00)	1.00 (0.500-1.02)	1.00 (0.500-2.00)	1.00 (0.500-2.00)
$t_{½}$, hr	NR	4.55 ± 1.81	3.85 ± 1.16	4.36 ± 2.41	7.52 ± 2.82	6.81 ± 1.99

[a] Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ± SD for $t_{½}$.
N = Number of subjects in the treatment group and contributing to the mean; n= number of subjects where $t_{½}$, AUC_{inf} were determined; NR = Not reported.
Summary statistics are not presented if fewer than 3 subjects have reportable parameter values.

On Day 10 of multiple-dose administration, PF-06700841 was absorbed rapidly with median T_{max} of 1.5 hours or less across the entire range of doses, from a total daily dose of 30 mg up to 175 mg. Following attainment of C_{max}, the disposition of PF-06700841 was similar with that observed following single-dose administration. Mean terminal $t_{½}$ ranged from 4.9 to 10.7 hours. In general, both AUC_{tau} and C_{max} appear to increase proportionally with dose from 10 mg to 175 mg. The mean apparent clearance (CL/F) was 10.8 L/hr to 23.7 L/hr, and the mean apparent volume of distribution (Vz/F) was 106.2 L to 249.4 L.

Table 2. Summary of Steady State Plasma and Urine PF-06700841 Pharmacokinetic Parameters Following Multiple Dose Administration, Study B7931001

	PF-06700841 Parameter Summary Statistics[a] by Treatment				
Parameter, units	**10 mg (QD)**	**30 mg (QD)**	**100 mg (QD)**	**50 mg (BID)**	**175 mg (QD)**
N, n	5, 5	3, 3	6, 6	4, 4	4, 4
AUC_{τ}, ng.hr/mL	422.8 (41)	1880 (52)	6089 (38)	3560 (35)	16180 (15)
C_{max}, ng/mL	63.4 (11)	286.6 (17)	734.1 (29)	522.0 (31)	2091 (28)
T_{max}, hr	1.0 (1.0-1.0)	1.00 (1.00-1.00)	1.5 (1.0-2.0)	1.0 (1.0-2.0)	0.98 (0.50-2.0)
CL/F, L/hr	23.7 (41)	16.0 (51)	16.4 (38)	14.0 (35)	10.8 (16)
t½, hr	5.93 ± 3.333	4.86 ± 1.93	10.67 ± 1.84	9.13 ± 2.26	7.46 ± 2.16
V_z/F, L	177.6 (30)	106.2 (12)	249.4 (45)	180.9 (30)	112.4 (18)
Ae_{τ}%	11.1 (45)	9.33 (57)	7.15[a]	15.5 (57)	8.91 (44)
CLr, mL/min	43.7 (18)	24.8 (15)	30.5[a]	36.3 (31)	16.0 (58)

[a] N=1.

Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ± SD for t½.
N = Number of subjects in the treatment group and contributing to the mean; n= number of subjects where t½ was determined.
AUC_{τ}, = Area under the concentration-time curve from zero to 24 hours (QD) or zero to 12 hours (BID) postdose at steady state; BID = Twice daily; C_{max} = Peak plasma concentration; CL/F = apparent total body clearance; CLr = Renal clearance; Ae_{τ}% = Percent of dose recovered unchanged in urine over the dosing interval τ; QD = Once daily; V_z/F = apparent volume of distribution.

Urinary recovery of PF-06700841 was low, with approximately <16% of the dose recovered unchanged in urine on Day 10 across all doses (geometric mean Ae_{τ}% of 8.9% to 15.5%). Renal clearance ranged from 16.0 mL/min to 43.7 mL/min.

The relative bioavailability (B7931001) of 100 mg PF-06700841 tablets compared to 100 mg oral suspension was 96.2% for AUC_{inf} and 94.3% for C_{max}. Both of the 90% CIs for the ratio were within the 80% to 125% equivalence interval. When the 100 mg tablets were administered under fed conditions, T_{max} was delayed with a median value of 4.0 hours, compared to a median T_{max} 0.5 hours under fasted conditions. For 100 mg tablets fed vs. fasted, the ratio (90% CI) of adjusted geometric means for AUC_{inf} and C_{max} was 82.3% (73.5%, 92.3%) and 64.3% (56.0%, 73.8%), respectively.

Listed in Table 3 are the PK parameters following multiple-dose administration of PF-06700841 to psoriasis subjects. PF-06700841 was absorbed rapidly with median T_{max} of 1 hour to 2 hours post dose. Mean terminal t½ was 16 hours in the 30 mg group and 6 hours in the 100 mg group. The mean t½ value in the 30 mg group includes a reported t½ value of 87.5 hours for one subject with an anomalous data point at 216 hours postdose: all other subjects in the dose group had concentrations below the lower limit of quantification (LLOQ) after 24 hours, and t½ values of 6.48 hours or less.

Table 3. Summary of Plasma PF-06700841 Pharmacokinetic Parameters Following Multiple Dose Administration in Psoriasis Subjects, Study B7931001

	Parameter Summary Statistics[a] by Treatment	
Parameter, units	**PF-06700841 30 mg QD (P)**	**PF-06700841 100 mg QD (P)**
N, n	7, 7	5, 5
AUC_τ, ng.hr/mL	990.0 (103)	7672 (43)
C_{max}, ng/mL	204.7 (43)	924.2 (13)
T_{max}, hr	1.00 (0.983-2.00)	2.00 (1.00-2.00)
CL/F, L/hr	30.30 (103)	13.04 (43)
MRT, hr	6.072 (92)	8.534 (36)
PTF	3.414 (44)[b]	2.654 (42)
t½, hr	16.01 ± 31.58	6.032 ± 1.712
V_z/F, L	245.4 (206)	109.6 (18)

[a] Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ± SD for t½.
[b] 4 subjects contributing to the mean in this group.
N = Number of subjects in the treatment group and contributing to the mean; n= number of subjects where t½, Vz/F and MRT were determined.

In general, dose normalized exposure was higher in the 100 mg group than in the 30 mg group although the highest individual dose normalized values for both AUC_τ and C_{max} were observed in one subject in the 30 mg group. Note that the subject in the 30 mg group with the highest C_{max} and AUC_τ values (Subject 10011092) is not the same subject with the anomalous 87.5 hour t½ value (Subject 10011117).

1.6. Study Rationale

This multicenter, placebo controlled study is being conducted to provide additional PF-06700841 safety and tolerability data, and to further explore the clinical efficacy of PF-06700841 in the treatment of moderate to severe plaque psoriasis following clinical results from the B7931001 Phase 1 study. Additionally, the study is intended to enable selection of oral dose and dosing regimen (daily vs. weekly chronic administration) for the future clinical development of PF-06700841. The current nonclinical toxicology package supports the planned treatment duration of up to 12 weeks.

The completed B7931001 Phase 1 study included Single Ascending Dosing (SAD) and Multiple Ascending Dosing (MAD) in healthy volunteers, Proof of Mechanism (PoM) and small efficacy investigations in patients with psoriasis. The study demonstrated acceptable safety and PK profile at single PF-06700841 doses from 1 to 200 mg, and once daily doses (QD) from 10 to 175 mg, and 50 mg twice daily (BID) for ten days. Dose escalation stopping rules were not triggered at any dose level during the SAD/MAD investigations. Additionally, clinical benefit was seen in subjects with chronic plaque psoriasis as measured by the change from baseline in PASI scores over the 28 day treatment period. In subjects completing through study Day 28, the mean placebo adjusted change from baseline in PASI score at Week 4 was -9.6 for the 30 mg cohort (n=7), and -14.2 for the 100 mg cohort (n=5). Sustained efficacy was observed at approximately 1 month after last dose of 100 mg PF-06700841, and approximately 1 week after the last dose of PF-06700841 30 mg, both dose levels administered QD over 28 days. This-suggests that less frequent dosing may offer

patients clinical benefit. The current B7931004 study design will test both daily and weekly dosing regimens (Figure 1).

The total treatment duration of 12 weeks in B7931004 will allow further exploration of the clinical efficacy observed in the 4 week small efficacy study completed in the Phase 1 study B7931001. Continuous change from baseline in PASI score at Week 12 will be used as the primary endpoint to gain sensitivity and efficiency regarding statistical power. The once daily PF-06700841 induction doses to be explored in the current study will be below the 100 mg dose level, (eg, 30 mg and 60 mg) in order to adequately evaluate clinical efficacy while minimizing safety risk. To further improve the risk/benefit, the study will explore a step down maintenance daily dosing with PF-06700841 10 mg and 30 mg for 8 weeks after the initial 4 week dosing with 30 mg or 60 mg QD. PF-06700841 100 mg once weekly (QW) will also be investigated in order to evaluate the clinical utility of a weekly maintenance dosing in subjects with plaque psoriasis.

Given the assumed PF-06700841 mediated inhibition of creatinine transport in the kidney, the inclusion of serum cystatin –C collection at baseline, end of treatment, and as indicated during the trial (see Section 7.1.3) will facilitate calculation of eGFR at these time points to provide a reliable assessment of renal function.

1.7. Dose Rationale

The dose selection strategy was designed to balance pharmacology and safety. A global PK model was developed using the data from the first-in-human study (Protocol B7931001). PK was assumed to be similar between healthy subjects and psoriasis subjects. The activity of the JAK inhibitors was assessed by measurement of various PD markers and markers of safety that were collected in the FIH study and analyzed using indirect response modeling. The magnitude of change in these markers required for efficacy and/or safety is poorly understood.

The predicted PK parameters for PF-06700841 based on simulations using the global PK model and predicted PD during the induction period (4 weeks) are provided in Table 4.

Table 4. Summary of Predicted Total Geometric Mean Plasma PF-06700841 Pharmacokinetic and Pharmacodynamic Parameters During the Induction Period of Multiple Dose Administration

Dose mg QD	Total C_{max} ng/mL	Predicted Margins Cmax[a]	Total AUC_{tau} ng.hr/mL	Predicted Margins AUC[a]	Percent Reduction from Baseline			
					hsCRP	IP-10	Neutrophils	Reticulocytes
Induction (4 weeks)								
30	206.7 (27)	15	1619 (44)	9.1	80 (7.5)	44 (29)	23 (66)	33 (40)
60	433.3 (27)	7.2	3797 (43)	3.9	84 (6.4)	51 (21)	32 (70)	50 (34)

[a] 9 month oral monkey NOAEL-20 mg/kg; mean male and female C_{max}(free) = 2263 ng/mL; C_{max} (total) = 3100 ng/mL; AUC_{tau} (free) = 10731 ng•h/mL; AUC_{tau} (total) = 14700 ng•h/mL, monkey (fu) = 0.73; human fu = 0.61

AUC_{tau} = Area under the concentration-time curve from zero to 24 hours postdose at steady state; C_{max} = Peak plasma concentration; QD = Once daily; ( ) = Coefficient of variation expressed as a percentage.

The predicted exposure based on total drug during the induction period at the maximum dose of 60 mg QD for 4 weeks is projected to maintain approximately a 7.2- and 3.9-fold safety margins for C_{max} and AUC_{tau}, respectively.

In Study B7931001, mechanistic biomarkers of efficacy eg hsCRP and IP-10 related to IL-6 and IFN-gamma, respectively, were measured in healthy subjects. Based on indirect response modeling, the predicted percent reductions in the hsCRP levels during the induction period ranged between 80% and 84% over the dose range 30-60 mg. Similarly, the reduction of IP-10 levels ranged between 44% and 51% over the same dose range. Modeling and simulations predicted maximum reductions in neutrophils and reticulocytes of 32% and 50%, respectively following 60 mg QD.

The predicted PK parameters for PF-06700841 based on simulations using the global PK model and predicted PD during the chronic dosing period (8 weeks) are provided in Table 5.

Table 5. Summary of Predicted Geometric Mean Total Plasma PF-06700841 Pharmacokinetic and Pharmacodynamic Parameters During the Chronic Period of Multiple Dose Administration

Induction Dose mg QD	Chronic Dose mg	Total C_{max} ng/mL	Predicted Margins C_{max}[a]	Total AUC_{tau} ng.hr/mL	Predicted Margins AUC[a]	Percent Reduction from Baseline			
						hsCRP	IP-10	Neutrophils	Reticulocytes
Chronic Dosing (8 weeks)									
30	30 QD	206.7 (27)	15	1619 (44)	9.1	81 (9.6)	45 (29)	28 (50)	34 (40)
30	10 QD	57.1 (29)	54	418.7 (44)	35	71 (19)	31 (38)	14 (48)	15 (43)
30	100 QW	746.8 (28)	4.2	6709 (45)	2.2	59 (28)	28 (46)	15 (55)	15 (41)
60	Placebo	NA	NA	NA	NA	NA	NA	NA	NA
60	10 QD	60.2 (30)	51	455.9 (45)	32	73 (20)	33 (37)	15 (42)	15 (41)
60	30 QD	200.5 (28)	15	1675.9 (43)	8.8	82 (7.7)	47 (26)	30 (45)	36 (35)
60	100 QW	727.0 (28)	4.3	6242 (45)	2.4	58 (26)	27 (40)	14 (51)	14 (44)

[a] 9 month oral monkey NOAEL-20 mg/kg; mean male and female C_{max}(free) = 2263 ng/mL; C_{max} (total) = 3100 ng/mL; AUC_{tau} (free) = 10731 ng•h/mL; AUC_{tau} (total) = 14700 ng•h/mL, monkey (fu) = 0.73; human fu = 0.61.

AUC_{tau} = Area under the concentration-time curve from zero to 24 hours postdose at steady state; C_{max} = Peak plasma concentration; NA = not applicable; QD = Once daily; QW = once weekly; ( ) = Coefficient of variation expressed as a percentage.

The 100 mg once weekly (QW) regimen during the chronic dosing period (8 weeks) was used to provide guidance as to the minimum projected safety margins during this period. The projected safety margins for C_{max} and AUC_{tau} are approximately 4.3- and 2.4-fold, respectively.

During the chronic dosing period the 30 mg QD induction and maintenance dose or the 60 mg QD induction dose followed by 30 mg QD are projected to reduce hsCRP and IP-10 by approximately 82% and 47%, respectively. These doses are projected to reduce neutrophils by approximately 30% and reticulocytes by 36%. The regimens that included 100 mg QW in the chronic dosing period are projected to reduce hsCRP and IP-10 by approximately 58% and 27%, respectively. The associated changes for neutrophils and reticulocytes are expected to be minimal (~14%). Overall, the doses selected for this study are expected to demonstrate clinically relevant efficacy in subjects with moderate to severe psoriasis.

1.8. Summary of Benefits and Risks

Overall, the safety profile observed during the Phase 1 program for PF-06700841 appears to be acceptable at dosages up to 175 mg administered orally as multiple doses over 10 days. A longer dosing duration was explored in psoriasis patients, who received the maximum PF-06700841 dose level of 100 mg daily for 28 days. No serious or severe AEs were reported in the Phase 1 study. However, there was one AE of herpes zoster infection in a psoriasis subject treated with 100 mg PF-6700841 for 4 weeks. As with other immunomodulators, the risk of infection is potential concern due to the immunosuppressive effects of PF-06700841. To limit this risk, a maximum daily dose below 100 mg (the dose associated with infection in the Phase 1 study B7931001) will be used in this Phase 2 trial. In addition, a variety of step down approaches including a weekly dosing will be tested in this study in order to identify a dose(s) and dosing regimen(s) with an acceptable risk /benefit profile.

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

CCI

[redacted]

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective(s):	Primary Endpoint(s):
• To evaluate the efficacy of PF-06700841 in moderate to severe plaque psoriasis.	• Change from baseline in PASI score at Week 12.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To explore the efficacy of PF-06700841 induction and maintenance dosing regimens in moderate to severe plaque psoriasis.	• Key secondary: Proportion of subjects achieving a PASI 75 response at Week 12. • Proportion of subjects achieving 50%, 75% and 90% reduction from baseline PASI at time-points specified in the SoA. • Change from baseline in PASI scores at time-points specified in the SoA. • Percent change from baseline in PASI scores at time-points specified in the SoA. • Change from baseline in PASI score at Week 4.
• To assess the safety and tolerability of PF-06700841 induction and maintenance dosing regimens.	• Incidence and severity of adverse events, serious adverse events and withdrawals due to adverse events. • Change from baseline in clinical laboratory values (chemistry and hematology, lipids). • Change from baseline in vital signs (blood pressure, pulse rate, oral or tympanic temperature measurements). • Change from baseline in ECG parameters (heart rate, QT, QTc, PR and QRS intervals).
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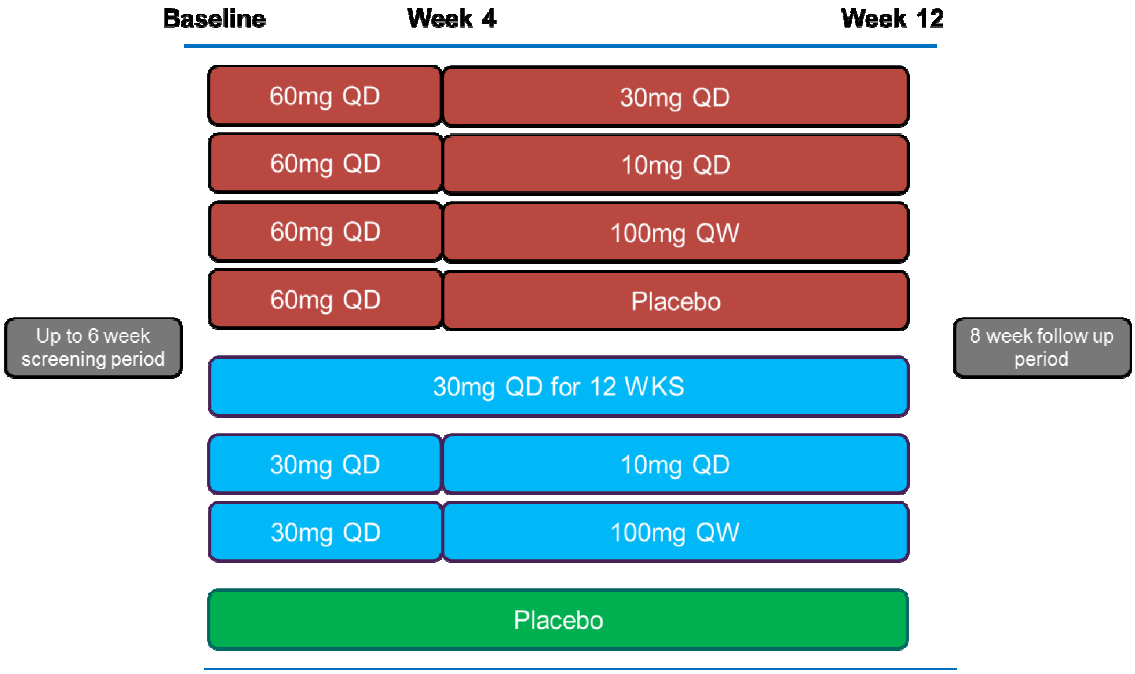
3. STUDY DESIGN

This is a Phase 2a, randomized, double-blind, placebo-controlled, parallel group, multicenter study in subjects with moderate to severe plaque psoriasis. The first part of the study, following a screening period (up to 6 weeks), is a 4 week induction period with double blind daily treatment. At the end of Week 4, all subjects switch to their predefined double blind maintenance treatment regimen for Week 5 through Week 12.

Approximately 200 subjects are planned to be randomized into the study, to allow for approximately 160 evaluable subjects (20 completers per arm). The randomization ratio will be 7:1, active: placebo. During the first 4 week treatment period, 2 oral daily dose levels (30 mg and 60 mg) of PF-06700841, plus matching placebo, will be investigated. During the 8 week maintenance treatment period (Weeks 5 through 12), subjects will receive either 10 mg or 30 mg PF-06700841 once daily, or a 100 mg once weekly regimen of PF-06700841, or matching placebo. Maintenance dose level and regimen will be assigned at the initial time of randomization into the study. All subjects, regardless of assigned regimen (ie, QD or QW) will receive blinded QD dosing throughout the study treatment period to maintain the study blind.

The duration of study subject participation will be approximately 26 weeks, including screening, 12 week treatment period, and 8 week follow up period.

Figure 1. Study Schematic



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.

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

4.1. Inclusion Criteria

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

1. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

2. Willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.

3. Male or female subjects between 18 and 75 years of age, inclusive, at time of informed consent.

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

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

6. Have plaque-type psoriasis covering at least 10% of total body surface area (BSA) at Baseline/Day 1 (prior to first dose of study drug).

7. Considered by investigator to be a candidate for systemic therapy or phototherapy of psoriasis (either naïve or history of previous treatment).

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

    - 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 postmenopausal state;

    - Have undergone a documented hysterectomy and/or bilateral oophorectomy;

    - Have medically confirmed ovarian failure.

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

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

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

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

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

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

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

    - Ustekinumab (Stelara®).

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

    a. Adalimumab (Humira®);

    b. Certolizumab pegol (Cimzia®);

    c. Infliximab (Remicade®);

    d. Alefacept (Amevive®).

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

    a. Etanercept (Enbrel®);

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

    c. Psoralen + UVA phototherapy (PUVA).

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

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

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

- UVB (narrowband or broadband) phototherapy.

4.2. Exclusion Criteria

Subjects 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, with the exception of nail psoriasis which is allowed.

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

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

4. 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.

5. Cannot discontinue systemic therapies and/or topical therapies for the treatment of psoriasis and cannot discontinue phototherapy (UVB or PUVA).

6. Are taking or require oral or injectable (eg, intraarticular, intramuscular or intravenous) corticosteroids for any condition.

7. 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 5).

- 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 6) total score ≥8.
- Clinically significant depression: patient health questionnaire – 8 items (PHQ-8) (Appendix 7) 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.

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:
   - Hemoglobin <11.0 g/dL or hematocrit <30% (<0.30 v/v);
   - Absolute neutrophil count of <2.5 x 109/L (<2500/mm^3);
   - Platelet count <100 x 109/L (<100,000/mm^3);
   - Serum creatinine level above the upper limit of normal (ULN) at Screening or an Estimated creatinine clearance Filtration Rate (GFR) value ≤80 mL/min based on the Cockcroft-Gault calculation at Screening (Appendix 2, Cockcroft-Gault equation);
   - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values greater than 2 times the upper limit of normal (ULN);
   - Any uncontrolled clinically significant laboratory abnormality that would affect interpretation of study data or the subject's participation in the study.
9. Pregnant female subjects; breastfeeding female subjects; fertile male subjects and female subjects of childbearing potential who are unwilling or unable to use 2 highly effective methods 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.
10. Have current or recent history of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiovascular, or neurological disease.

11. Have a history of any lymphoproliferative disorder (such as Epstein Barr Virus [EBV] –related lymphoproliferative disorder, history of lymphoma, leukemia, or signs and symptoms suggestive of current lymphatic disease.

12. Have a history (single episode) of disseminated herpes zoster or disseminated herpes simplex, or a recurrent (more than one episode of) localized, dermatomal herpes zoster.

13. Have a history of infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator within 6 months prior to first dose of study drug.

14. Have a history of infection requiring oral antimicrobial therapy within 2 weeks prior to first dose of study drug.

15. Infected with Mycobacterium tuberculosis (TB) as defined by the following:

    a. A positive Interferon Gamma Release Assay (IGRA) test performed at or within the 12 weeks prior to Day 1 is exclusionary; a negative test is required for eligibility. The following are acceptable IGRA assays: QuantiFERON® - TB Gold test (QFT-G), QuantiFERON® - TB Gold In-Tube test (QFT-GIT) and T-SPOT®.

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

       - Subjects with repeat indeterminate IGRA results may be enrolled after consultation with pulmonary or infectious disease specialist that determines low risk of infection (ie, subject would be acceptable for immunosuppressant treatment without additional action).

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

    b. Chest radiograph taken at screening with changes suggestive of active TB infection, unless previously performed normal and documented chest radiograph within 12 weeks prior to Day 1.

    c. A history of either untreated or inadequately treated latent or active TB infection.

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

16. Have been vaccinated with live or attenuated live vaccine within the 6 weeks prior to the first dose of study drug, or expects to be vaccinated with these vaccines during treatment, or within the 8 weeks following the last dose of study drug. (For further information regarding avoidance of household contacts who may be vaccinated see Section 5.8.4).

17. Any cell-depleting agents including but not limited to rituximab within 6 months of first dose of study drug or 5 half-lives (if known), whichever is longer, or until lymphocyte count returns to normal, whichever is longer.

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

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

20. Have previously been treated with secukinumab (Cosentyx) or Ixekizumab (Taltz).

21. Have undergone treatment with tofacitinib within 3 months of first dose.

22. Have undergone treatment with apremilast (Otezla) within 3 months of first dose.

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

24. Have a history of alcohol or substance abuse, unless in full remission for greater than 6 months prior to first dose of study drug.

25. Have a Screening or Baseline/Day 1 12-lead ECG that demonstrates clinically relevant abnormalities which may affect subject safety or interpretation of study results.

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

27. 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 or cervical carcinoma in situ.

28. Any medical history of disease [ie, Gilbert's 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.

29. Have undergone significant trauma or major surgery within 1 month prior to Screening.

30. Require treatment with prohibited concomitant medications(s) (see Appendix 4) including prohibited dietary supplements (see Section 5.8.3) or have received a prohibited concomitant medication/dietary supplement within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study drug. Note: amiodarone requires discontinuation at least 290 days (~5 half-lives) prior to the first dose of study drug.

31. Infected with hepatitis B or hepatitis C viruses; for Hepatitis B, all subjects will undergo testing for Hepatitis B Surface Antigen (HBsAg) and Hepatitis B Core Antibody (HVcAB). Subjects who are HBsAg positive are not eligible for the study. Subjects who are HBsAg negative and HBcAb positive will be reflex tested for Hepatitis B Surface Antibody (HBsAb) and if HBsAb is positive, may be enrolled in the study; if HBsAb is negative, the subject is not eligible for the study. Subjects who are HCV Ab positive require further testing with HCV RNA PCR. Subjects with false positive anti-HBc may be enrolled based upon consultation with hepatologist confirming no infection with hepatitis B.

32. Participation in other studies using an investigational or experimental therapy or procedure within 4 weeks or 5 half-lives (whichever is longer) before the study begins and/or during study participation. *Exception: any investigational or experimental therapy or procedure for psoriasis, psoriatic arthritis or rheumatoid arthritis must be discontinued for at least 12 weeks prior to first dose of study drug. Exposure to investigational biologics should be discussed with the Pfizer Medical Monitor (or designee).* Subjects cannot participate in studies of other investigational or experimental therapies or procedures at any time during their participation in this study.

33. Other acute or chronic medical or psychiatric condition 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.

34. 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.

35. Refrain from 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.

36. Subjects who received or are likely to receive during the study any moderate-strong inhibitors eg, itraconazole, erythromycin, ketoconazole, protease inhibitors, verapamil or diltiazem or inducers eg rifampin of CYP3A4.

4.3. Lifestyle Requirements

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

- On appropriate study visit days, comply with fasting requirement (water only) for at least 8 hours prior to the visit, as indicated in the Schedule of Activities.
- On study visit days, do not smoke or ingest caffeine (eg, tea, coffee, some soft drinks/colas/energy drinks and power bars) during the 30 minutes prior to blood pressure and pulse (heart) rate measurements.
- On study visit days, do not take the morning dose of study drug until instructed to do so by the investigator or designated study site staff.
- On study visit days, showering or bathing is permitted prior to attending the study visit, but do not moisturize.
- On study visit days, take prescribed permitted concomitant medication, as needed, prior to the study visit, if it can be administered with water only. Prescribed permitted concomitant medications that must be taken with food or after meals should not be taken until after the visit procedures have been completed.
- Discontinue and avoid using certain medications and treatments (see Inclusion Criteria and list of prohibited concomitant medications in Section 4.1, Section 5.8.2 and Appendix 4).
    - Contact the study site investigator if there are any changes or additions to concomitant medications.
- Refrain from 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.
- Avoid having elective surgery.
- Agree to use proper contraceptive methods (See Section 4.3.1).
- As needed, subjects may use the treatments listed as permitted in Section 5.8 for the specified body sites described. On clinic visit days, do not use any of these treatments until after the clinic visit is completed.

4.3.1. Contraception

In this study, fertile male subjects and female subjects who are of childbearing potential as applicable to the study will receive PF-06700841, which has been associated with demonstrated teratogenicity/fetotoxicity in animals. Subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use 2 methods of highly effective contraception throughout the study and for at least 28 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected 2 appropriate methods of contraception for the individual subject and his/her partner(s) from the list of permitted contraception methods (see below) and will confirm that the subject has been instructed in their 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 2 highly effective methods of contraception consistently and correctly and document the conversation, and the subject's affirmation, in the subject's chart. In addition, the investigator or designee will instruct the subject to call immediately if 1 or both of the selected contraception methods 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 and correctly (ie, perfect use) and include the following:

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 investigational product.

4.4. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the Study Binder.

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. 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 is PF-06700841. The designation PF-0670841-15 indicates a salt of the drug substance. References to either PF-06700841 or PF-0670841-15 indicate the same biological entity.

5.1. Allocation to Treatment

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

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

5.2. Breaking the Blind

At the initiation of the study, the investigator site will be instructed on the method for breaking the blind. The method will be an electronic process. Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the subject. Investigators are encouraged to discuss with a member of the study team if they believe that unblinding is necessary. When the blinding code is broken, the reason must be fully documented and entered on the case report form (CRF).

5.3. Subject Compliance

For self-administration of PF-06700841-15 tablets at home, compliance will be captured and completed by the subject on a dosing diary. Subject compliance will be verified by the accounting of investigational product at each visit. When investigational product is administered at the research facility, it will be administered under the supervision of study personnel.

5.4. Investigational Product Supplies

5.4.1. Dosage Form(s) and Packaging

Blinded PF-06700841-15 tablets and matching placebo will be provided as tablets for oral administration. The PF-06700841-15, 5 mg and 25 mg tablets and their matching placebos will be supplied in blisters and labeled according to local regulatory requirements.

5.4.2. Preparation and Dispensing

The investigational product will be dispensed using an IRT drug management system at each visit from Week 0 to Week 10. A qualified staff member will dispense the investigational product via unique container numbers in the blister cards provided, in quantities appropriate for the study visit schedule. The subject/caregiver should be instructed to maintain the product in the bottle (or blister cards, as appropriate) provided throughout the course of dosing and return the bottle (or blister cards, as appropriate) to the site at the next study visit.

5.5. Administration

Subjects will receive investigational product (IP) as outpatients. PF-06700841-15 tablets and matching placebo for oral administration will be dispensed in blisters. Subjects will be provided dosing instructions.

All subjects, regardless of assigned treatment regimen (ie, QD or QW) will receive blinded QD dosing throughout the study treatment period to maintain the study blind.

Sites will be trained on how subjects should take tablets at home through an IP manual and/or other vehicle(s). Sites are responsible for communicating this information.

Subjects should take the medication orally for 12 weeks from study Days 1 to 85 during the trial; Subjects should swallow the tablets with ambient temperature water to a total volume of approximately 240 mL; Subjects will swallow the investigational product whole, and will not

manipulate or chew the medication prior to swallowing; IP may be taken with or without food; however, for **study visit days**, subjects are to be instructed to refrain from dosing at home, and are to take the dose in the clinic from their previous blister card and dose from the newly dispensed blister card on the next day at home.

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

5.6. Investigational Product Storage

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

Investigational products should be stored in their original containers and in accordance with the labels.

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.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

Site staff will instruct subjects on the proper storage requirements for take home investigational products.

5.7. Investigational Product Accountability

Drug Accountability procedures are to be performed at Weeks 1, 2, 4, 6, 8, 10, 12, and at the end of treatment Early Termination visit.

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.

Subjects must be instructed to return all blister cards of study drug (and any unused study drug) to the investigator at every visit and at the end of the trial.

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)

5.8.1. Permitted Concomitant Medication

Concomitant psoriasis therapies are not permitted during the study, with the exception of:

Table 6. Permitted Topical Concomitant Psoriasis Treatments

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

5.8.2. Prohibited Concomitant Medications

The following hydrocortisones are NOT permitted:

- Hydrocortisone 17 butyrate.
- Hydrocortisone valerate.
- Hydrocortisone/hydrocortisone acetate with concentration higher than 1%.

Subjects will abstain from all concomitant medications as described in the Inclusion and Exclusion sections of the protocol and Appendix 4 Prohibited Concomitant Medications.

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

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

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

A subject who is receiving digoxin or metformin as concomitant medication must allow at least two hours after taking either medication and before taking study medication.

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

5.8.3. Dietary Supplements

For the purposes of this protocol, dietary supplements are defined as vitamins, minerals, purified food substances, and herbals with pharmaceutical properties. Vitamins, minerals and purified food substances are allowed in amounts not known to be associated with adverse effects (such as hypervitaminosis).

Herbals supplements are only allowed on a case by case basis; please contact the Pfizer staff. Herbals eg, St. John's Wort that are known to have an effect on drug metabolism must be discontinued at least 4 weeks or 5 half-lives (whichever is longer) before the first dose of investigational product.

5.8.4. Vaccinations

Vaccination with live virus, attenuated live virus, or any live viral components is prohibited within the 6 weeks prior to the first dose of study drug, during the study, and for 8 weeks after the last dose of study medication. Similarly, current routine household contact with individuals who have been vaccinated with live vaccine components should be avoided during treatment and for 8 weeks following completion of treatment.

Such vaccines include: FluMist® (intranasal influenza vaccine), attenuated rotavirus vaccine, varicella (chickenpox) vaccine, attenuated typhoid fever vaccine, oral polio vaccine, MMR (measles, mumps, rubella) vaccine and vaccinia (smallpox) vaccine. Following vaccination with live component vaccines, the virus may be shed in bodily fluids, including stool, and there is a potential risk that the virus may be transmitted.

5.9. Rescue/Escape Medication

Permitted Topical Concomitant Psoriasis Treatments can be found in Section 5.8.1.

6. STUDY PROCEDURES

6.1. Screening

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

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.

6.4. 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 study site (see Schedule of Activities for procedures to be followed at the Early Withdrawal Visit).

Subjects who withdraw from the study may be replaced at the discretion of the investigator upon consultation with the sponsor.

For subjects who discontinue early from the double-blind treatment period prior to the Week 12 visit, the procedures scheduled for Week 12 will be performed on the last day the subject takes the investigational product or as soon as possible thereafter. For subjects who discontinue early from the follow up period prior to the Week 16 visit, the procedures scheduled for Week 16 will be performed at the Early Termination visit.

See Appendix 3 for Guidelines for Safety Monitoring and Discontinuations.

6.4.1. Withdrawal of Consent

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.

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 post-treatment study follow-up, and entered on the appropriate 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.

6.4.2. Lost to follow-up

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 below. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter.

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.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. 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 adverse events (AEs).

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will 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 this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will 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 Assessments

Standard safety assessments include physical examination, vital signs, 12-lead electrocardiogram (ECG), clinical laboratory evaluations (full and abbreviated chemistry panel), lipid panel, and urinalysis. Subject safety monitoring and discontinuation guidelines are provided in Appendix 3.

7.1.1. Laboratory

The following safety laboratory tests will be performed at times defined in the Schedule of Activities.

Laboratory Tests

Hematology	Chemistry	Urinalysis[j]	Other
Hemoglobin	BUN/Urea and	pH	FSH[f,g]
Hematocrit	Creatinine	Glucose (qual)	β-hCG[h]
RBC count	Cystatin C[a]	Protein (qual)	Hepatitis B, C and HIV[g]
Platelet count	Glucose	Blood (qual)	QFT-G or other IGRA[g]
WBC count	Calcium	Ketones	hsCRP
Total neutrophils	Sodium	Nitrites	IP-10
(Abs)	Potassium	Leukocyte esterase	CCI
Eosinophils (Abs)	Chloride	Microscopy[e]	
Monocytes (Abs)	AST, ALT		
Basophils (Abs)	Total Bilirubin		CCI
Lymphocytes (Abs)	Direct bilirubin[b]		
Reticulocytes (Abs)	Alkaline phosphatase		
PT/INR/PTT	Uric acid		
	Albumin		
	Total protein		CCI
	Creatine kinase (CK)		
	CK fractionation[c]		
	Total Cholesterol[d]		
	Triglycerides[d]		CCI
	HDL[d]		
	LDL[d]		
			CCI

a. At baseline, end of study, and when creatinine is elevated above ULN.
b. Only if total bilirubin is elevated.
c. Only if CK is elevated.
d. Fasting (water only), 8 hours prior to collection.
e. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase. Urine culture is performed if urinalysis is positivie for nitrite and/or leukocyte esterase or if clinically indicated.
f. In females who are amenorrheic for at least 12 consecutive months.
g. Complete at screening.
h. If serum pregnancy test is borderline positive, the central lab will run a FSH test to confirm menopause, assuming other menopause criteria are met per protocol eligibility requirements.
i. [redacted]
j. Dipstick in all cases.

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 serum 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. 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.[16]

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.[17,18] 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 CKD-EPI creatinine, cystatin C, or creatinine-Cystatin C equations.[19]

Serum creatinine will be measured as part of serum chemistry at times specified in the Schedule of Activities section of the protocol. Serum creatinine based eGFR will be calculated. Serum cystatin C and cystatin C based eGFR will be measured at baseline and end of treatment (EOT). An increase in serum creatinine above the upper limit of normal (ULN) as defined by the laboratory reference range should trigger a reflex test for serum cystatin-C in order to facilitate both cystatin C based and serum creatinine based eGFR calculations.

7.1.4. 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 for all subjects, in order to facilitate calculation of eGFR at these time points. When cystatin-C reflex testing is performed, corresponding serum creatinine and cystatin-C based eGFR will be determined to assess renal function.

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.[20]

7.1.5. Interferon Gamma Release Assay Tuberculin Test

Subjects may be screened for TB using an IGRA per local guidelines. Interferon gamma release assay will be tested during screening or within 12 weeks prior to Day 1. The following are acceptable IGRA assays: QuantiFERON®-TB Gold test (QFT-G), QuantiFERON®-TB Gold In-Tube test (QFT-GIT) and T-SPOT® TB test. Site personnel should follow the processing and analyses steps based on the assay chosen. Ensure incubation steps are followed as appropriate.

An IGRA is preferred for subjects with a prior Bacillus Calmette-Guerin (BCG) vaccination, but may be used for any subject. Documentation of IGRA product used and the test result must be in the subject's source documentation.

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

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

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

Refer to lab manual for any additional processing information and shipping instructions.

7.1.6. Herpetiform Skin Rash Surveillance

For any occurrence of a suspected herpetiform rash (eg, herpes zoster and herpes simplex), additional specimens for viral DNA analysis will be obtained for confirmation. [redacted] Details for these collections will be provided in the laboratory manual.

7.1.7. Medical History, Physical Examination, Height and Weight

Medical history will be collected at the Screening visit and will include history of drug, alcohol and tobacco use. Medical history also includes collection of details on (i) Family history of diabetes mellitus, hypertension, and premature coronary heart disease (CHD), where premature CHD is defined as (a) CHD in a male first degree relative <55 years of age, or (b) CHD in a female first degree relative <65 years of age, (ii) Any prior rheumatologist confirmed diagnosis of psoriatic arthritis or rheumatoid arthritis, (iii) Any prior diagnosis of dry eye disease/syndrome, and (iv) Any previous history of liver biopsy. Smoking status and average weekly alcohol consumption (units/week) will also be collected, where a unit contains 12 g of pure alcohol, an amount equivalent to that contained in 5 oz (a glass) of wine, 12 oz of beer, or 1.5 oz of 90 proof of spirits.

Complete physical examinations must be performed by the investigator, sub-investigator, or a qualified healthcare professional per local guidelines. A complete physical examination will include general appearance, skin, head, eyes, ears, nose and throat (HEENT), heart, lungs, breast (optional), abdomen, external genitalia (optional), extremities, neurologic function, back, and lymph nodes.

Targeted physical examinations must be performed by the investigator, sub-investigator, or a qualified healthcare professional per local guidelines. Targeted physical examination consists of skin, heart, lungs, abdomen, and examination of body systems where there are symptom complaints by the subject.

Complete and Targeted physical examinations are performed at specified time points (see Schedule of Activities).

Height and weight will be measured without the subject wearing shoes. Height (inches or centimeters) will be measured and recorded at the Screening visit only and weight (lbs or kg) will be measured and recorded at various time points (see Schedule of Activities).

7.1.8. Vital Sign Measurements (Blood pressure, pulse rate, and temperature)

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

Vital signs should be performed before laboratory blood collection.

Sitting blood pressure will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mm Hg. It is preferred that the same arm (preferably the dominant arm) be used throughout the study.

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

It is preferred that body temperature be collected using tympanic, oral, or axillary methods and that the same method be used consistently throughout the study.

7.1.9. Electrocardiogram

Twelve (12) lead ECGs should be collected at times specified in the Schedule of Activities.

ECGs should be performed before laboratory blood collection.

All scheduled ECGs should be performed after the subject has rested quietly for at least 5 minutes in a supine position. 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, BP, and pulse rate.

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

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, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTc values are in the acceptable range.

7.1.10. Chest Radiograph

Chest x-ray (posterior-anterior and lateral views are recommended however local guidelines should be followed) or other appropriate diagnostic image (ie, computed tomography [CT] or magnetic resonance imaging [MRI]) with no current evidence of untreated latent or active TB infection or evidence of currently active TB, general infections, heart failure or malignancy taken at screening or within the 12 weeks prior to Day 1 and read by a qualified radiologist. Documentation of the official reading must be located and available in the source documentation.

7.1.11. Subject Diary

Subjects will be provided with a diary to record their daily dosing for all 12 weeks of treatment. CCI [redacted]

7.2. Efficacy Assessments

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

7.2.1. Psoriasis Area and Severity Index (PASI)

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.

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

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.[21]

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

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.

Calculation of PASI will be done centrally by Sponsor programmers.

7.2.2. 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

7.2.3. Physician Global Assessment (PGA)

The Physician Global Assessment of psoriasis is scored on a 5-point scale, reflecting a global consideration of the erythema, induration and scaling across all psoriatic lesions. Average erythema, induration and scaling are rated separately over the whole body according to a 5-point severity scale, scored from 0 to 4, with appropriate morphologic descriptors. The severity rating scores are summed and the average taken – the total average is rounded to the nearest whole number score to determine the PGA (See Appendix 8).

The 5-point scale for PGA is: 0, “clear”; 1, “almost clear”; 2, “mild”; 3, “moderate”; 4 “severe”.

7.2.4. Body Surface Area (BSA)

Assessment of body surface area involved in psoriasis is performed separately for four areas of the body: head, upper limbs, trunk, and lower limbs. The percentage surface area affected by psoriasis is estimated by means of the “handprint method”, where the full hand of the subject (ie, the subject’s flat hand, thumb and fingers) represents approximately 1% of the total BSA[22] and a set percentage of each of the four areas of the body:

- 1 handprint corresponds to approximately 10% of the head/neck.
- 1 handprint corresponds to approximately 5% of the arm/upper limbs.
- 1 handprint corresponds to approximately 3.3% of the trunk.
- 1 handprint corresponds to approximately 2.5% of the lower limbs.

The extent (%) to which each of the four areas of the body is affected is captured on the CRF (to 2 decimal places, as necessary). A weighting factor is applied to each of the four areas in calculation of the total body surface area affected: head x0.1; upper limbs x0.2; trunk x0.3; lower limbs x0.4, as the four areas correspond to approximately 10%, 20%, 30% and 40% of the total BSA, respectively.[22] The sum of the weighted percent involvement obtained for each of the four body areas is the overall psoriatic BSA.

7.2.5. Target Lesion and Regional Photography (at select study centers)

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.

Regional Photography: Regional photographs of each target lesion and surrounding area will also be taken at select study centers. 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 Week 0 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 Week 0, Week 4, Week 12/Early Termination, and follow-up visit Week 16/ Early Termination. Additional instructions related to target lesion and Regional Photography can be located in the study manual.

7.3. Patient Reported Outcomes

Patient Reported Outcomes (PRO) data will be collected using the CCI [redacted], an CCI [redacted] item, and a CCI [redacted]. The subject will complete the questionnaires at the clinic prior to other clinical activities or the administration of study medication. The amount of time required for subjects to complete the PRO questionnaires at each visit is approximately 10 minutes.

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

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

Patient health questionnaire – 8 items (Appendix 7) 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.

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

Suicidal behaviors questionnaire- revised (Appendix 6) 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.

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

7.4.1. High-Sensitivity C-Reactive Protein (hsCRP)

Blood samples for determination of hsCRP will be obtained at the times specified in the Schedule of Activities.

Instructions and supplies for collection, processing, and shipment of samples will be supplied under separate cover by Pfizer, the designated laboratory vendor, and the vendor laboratory manual.

7.4.2. Interferon Gamma-Induced Protein 10 (IP-10)

Blood samples for the analysis of IP-10 will be collected into appropriately labeled tubes containing no preservative, anticoagulant or serum separator according to the times outlined in the Schedule of Activities.

Instructions and supplies for collection, processing, and shipment of samples will be supplied under separate cover by Pfizer, the designated laboratory vendor, and the vendor laboratory manual.

[redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

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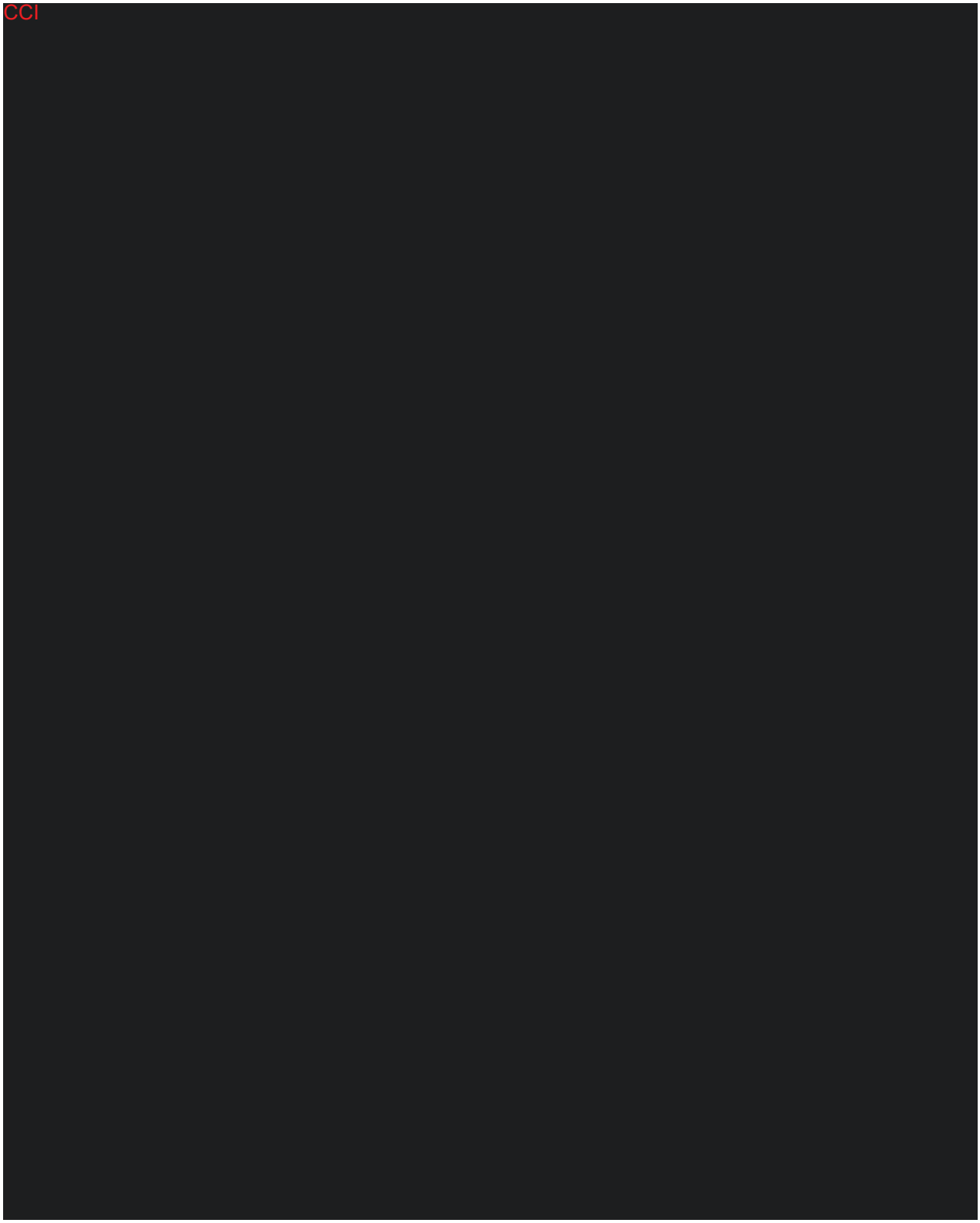

CCI [redacted]

CCI [redacted]

CCI [redacted]

7.7. Psychological Assessments

7.7.1. Columbia Suicide Severity Rating Scale (C-SSRS)

Columbia suicide severity rating scale is a validated tool to evaluate suicidal ideation and behavior (Appendix 5).

At Screening Visit and Baseline Visit, if there are "yes" answers on items 4, 5 or on any suicidal behavioral question of the C-SSRS, the subject will not be included in the study.

At any post-baseline visits, if there are "yes" answers on items 4, 5 or on any behavioral question of the C-SSRS, the subject will be discontinued from the study and referred to a mental health professional for appropriate evaluation and treatment.

If the subject cannot be seen by a mental health professional within 24 hours, then then subject should be sent to a local emergency room for psychiatric assessment.

7.8. Rater Qualifications

Clinical evaluations of psoriasis will be performed by an experienced and qualified dermatologist or other health professional with experience with PASI scoring after consultation and approval by the Sponsor.

The evaluator must receive and document protocol specific and applicable efficacy assessment scales training prior to performing these evaluations. **To assure consistency and reduce variability, the same evaluator should assess all PASI evaluations for any individual subject throughout the study whenever possible** (at a minimum, the same evaluator **must** perform the PASI assessment at baseline and at Week 12); a back-up experienced and qualified, protocol-trained evaluator will only be allowed and documented

in case of emergency or special situations when the designated evaluator is unable to perform the evaluation.

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/legally acceptable representative. In addition, each study subject/legally acceptable representative 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 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. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.4.2. 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.

8.4.3. Potential Cases of Decreased eGFR

In FIH study B7931001, blood creatinine elevation was reported across dose levels in healthy volunteer and psoriasis patients (Section 1.5.1).

Abnormal values in serum creatinine concurrent with absence of increase in blood urea nitrogen (BUN) that meet the below criteria, 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 in serum creatinine above the upper limit of normal (ULN) as defined by the laboratory reference range should trigger a reflex testing for serum cystatin-C in order to facilitate both cystatin C based and serum creatinine based eGFR calculations.

Based on these measurements, estimated GFR using serum creatinine and serum cystatin C will be determined at the time of elevation in serum creatinine above ULN. All subjects will also have serum creatinine based and serum cystatin-C based eGFR calculated at baseline upon entry into the study.

If an individual subject demonstrates a CONCOMITANT serum creatinine based AND serum 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 for a safety follow-up visit. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating serum creatinine and serum cystatin C, laboratory tests should also include: serum BUN, serum CK, serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, calcium), in addition to urine dipstick, urine microscopic examination, and urinary indices. All cases confirmed on repeat

testing as meeting the laboratory 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 serum creatinine.

All relevant test results will be forwarded to Pfizer for review immediately upon receipt by the PI.

This requirement applies to all subjects, all cohorts.

8.4.4. 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.

8.4.4.1. 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.

8.4.4.2. 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.

8.4.4.3. 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.

8.4.5. 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

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

9.1. Sample Size Determination

The sample size is based on the primary efficacy endpoint, PASI change from baseline at Week 12. With an assumption of standard deviation of 10, a total of 200 randomized subjects in the 8 treatment groups will provide approximately 95% power to detect a -11.8 placebo adjusted PASI change from baseline at Week 12 (difference between PF-06700841 and placebo) at significance level of 0.05 (one-sided) using Dunnet test for multiplicity adjustment. Approximately 160 completers (20 completers per treatment group) can be achieved with an assumption of 20% dropout rate.

9.2. Efficacy Analysis

The primary analysis is based on the classic PASI scores described in the sample size determination section.

Analysis of efficacy endpoints will be performed for the modified intent-to-treat (mITT) population, defined as all randomized subjects who receive at least 1 dose of investigational product.

All analyses will be detailed in the Statistical Analysis Plan (SAP).

9.2.1. Analysis of the Primary Endpoint

The primary endpoint is the change from baseline in PASI score at Week 12. The treatment effect in each of the active treatment groups is defined as the placebo adjusted change from baseline of the PASI score at Week 12 (mean change from baseline at Week 12 in the active treatment group minus the mean change from baseline at Week 12 in the placebo group). The estimates for treatment effect will be obtained by fitting the mixed-effect models repeated measures (MMRM) assuming missing at random to the PASI change from baseline score. The model will include treatment (active doses and placebo), visit, treatment by visit interaction as fixed effects and baseline value as a covariate. We will allow an unstructured variance-covariance matrix. Covariance matrices with other structure will be considered in sensitivity analysis. Estimates and the appropriate confidence intervals will be presented. All 7 active treatment groups will be compared with placebo, and Dunnet test will be used for multiplicity adjustment.

Analysis of covariance (ANCOVA) will be implemented as sensitivity analysis. This additional estimate of the treatment effect relies on the subset of observations (Week 12 and baseline). It is potentially less efficient than the estimate based on the MMRM but eliminates the complexity of modeling the covariance between the repeated measures of outcome observed at different visits. Estimates and the appropriate confidence intervals will be presented for each of these methods.

The linear PASI (L-PASI) score will be analyzed as additional sensitivity analysis using MMRM and ANCOVA.

In addition to the primary analysis based on the evaluating contrasts of the treatment effects, data permitting, dose-response relationship for the primary endpoint may be explored.

9.2.2. Analysis of Secondary Endpoints

Binary endpoints (ie, proportions of subjects achieving 50%,75% and 90% reduction from baseline PASI response rates and proportions of subjects with Physician Global Assessment of 'clear' or "almost clear") will be analyzed by reporting a proportion of subjects with the event of interest in each of the treatment groups at each visit. Estimate and 90% confidence interval for the difference of proportions (each of the active doses against placebo) will be calculated, using normal approximation to the distribution of the observed difference in proportions.

Logistic regression/odds ratio modeling approach will be employed as a sensitivity analysis unless the proportion of the events in one of the groups is too small for the applicability of this method.

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CCI [redacted]

9.6. Safety Analysis

All subjects who receive study medication (safety population) will be included in the safety analyses. All the safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations. Safety endpoints for the study include:

- On-treatment adverse events (AEs) and serious adverse events (SAEs).
- Withdrawals from active treatment due to AEs.
- Serious infections, defined as any infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials.
- Safety laboratory tests.
- Vital signs.
- ECG parameters.

Safety data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. A set of safety summary tables by treatment will be produced to evaluate any potential risk associated with the safety and toleration of administering the study medication, continuous outcomes (eg, blood pressure, heart rate etc) will be

summarized using N, Mean, Median, Standard Deviation etc. Categorical outcomes (eg, occurrence of any adverse event) will be summarized by subject counts and percentage. Change from baseline on laboratory data and vital signs will be additionally summarized.

Subject listings will also be produced for these safety endpoints. The safety endpoints will be listed and summarized in accordance with Pfizer Data Standards. The safety analyses will be carried out in the safety population, detailed analyses will be described in the SAP.

The analyses of adverse events under the 3-tier approach are considered exploratory. There will be no adjustment for multiple comparisons or stratification factor in the analyses unless specified.

Nominal p-values (Tier 1 events only) and 95% confidence intervals (Tier 1 and Tier 2 events) will be provided for between treatment differences in the percentage of subjects with events. Reporting p-values and confidence intervals will follow Pfizer standard practice in the 3-tier approach.

CCI [redacted]

CCI [redacted]

9.8. Data Monitoring Committee

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

CCI [redacted]

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

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct 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 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.

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/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 subject chart. In these cases, data collected on the CRFs must match the data in those charts.

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

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, and 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 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 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 law.

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, or his or her legally acceptable representative is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's legally acceptable representative, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative 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 a Member State

End of trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of subjects have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as last subject last visit (LSLV).

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-06700841 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 a time period set by Pfizer. 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 trial 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 (clinical study report synopses in which any data that could be used to identify individual patients has 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.

16. REFERENCES

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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
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BBS	Biospecimen Banking System
BP	blood pressure
CK	creatine kinase
CRF	case report form
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSR	clinical study report
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EU	European Union
EudraCT	European Clinical Trials Database
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HIV	human immunodeficiency virus
HRQL	health-related quality of life
ICH	International Conference on Harmonisation
ID	identification
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IWR	interactive web response
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LFT	liver function test

Abbreviation	Term
LSLV	last subject last visit
MnB	meningitidis serogroup B
N/A	not applicable
PCD	primary completion date
PD	Pharmacodynamics(s)
PFS	prefilled syringe
PGx	Pharmacogenomics(s)
PI	principal investigator
PK	pharmacokinetic
PT	prothrombin time
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
ULN	upper limit of normal
US	United States

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. Guidelines for Safety Monitoring and Discontinuation

The following protocol-specified guidelines for safety monitoring and discontinuation are to be implemented to all subjects in Study B7931004. Additional individual subject monitoring is at the discretion of the investigator and dependent on any perceived safety concerns. Unscheduled clinical labs may be obtained at any time during the study to assess such concerns, and a subject may be withdrawn at any time at the discretion of the investigator.

Appendix 3.1. Safety Monitoring

Subjects with the following laboratory abnormalities require prompt retesting within one week (preferably within 48 hours) from awareness of the abnormal results:

- Absolute neutrophil count <2000/mm^3;
- Hemoglobin <11.0 g/dL;
- Platelet count below <100,000/mm^3.

Subjects with the following laboratory abnormalities require prompt retesting within 72 hours (but preferably within 48 hours) from awareness of the abnormal results:

- Serum creatinine >upper limit of normal (ULN).
    - If serum creatinine > ULN (see protocol Section 7.1.3 and Section 8.4.3), measurement of serum cystatin C (reflex testing) will occur along with eGFR calculation. Decision to discontinue dosing will be based on eGFR, as described below in Appendix 3.2.
- For women of childbearing potential (any female subject who does not meet at least one of the criteria of non-childbearing potential listed in Section 4.1) with any positive or indeterminate point-of-service urine β-hCG test or with a missed menstrual period, the subject will have study drug interrupted and a serum sample submitted to the central laboratory for β-hCG testing. A subject may not progress further in the study unless pregnancy is ruled-out.

Additional individual subject safety monitoring not specified in these guidelines is at the discretion of the investigator and dependent on any perceived safety concerns. Unscheduled laboratory testing through the central laboratory may be obtained at any time during the study to assess such concerns, and a subject may be withdrawn at any time at the discretion of the investigator.

Appendix 3.2. Discontinuation

Treatment with PF-06700841 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 for treatment, or meeting other criteria that require the infection to be classified as a serious adverse event.

- Other serious or severe AEs, after consultation with the Pfizer clinician.

Potential Cases of Decreased eGFR:

If an individual subject demonstrates CONCOMITANT serum creatinine-based AND serum 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 (see protocol Section 8.4.3).

Psychological Assessment

At any post-baseline visits, if there are "yes" answers on items 4, 5 or on any behavioral question of the C-SSRS, the subject will be discontinued from the study and referred to a mental health professional for appropriate evaluation and treatment. **If the subjects cannot be seen by a mental health professional within 24 hours of initial assessment, then the subject should be sent to the local emergency room for psychiatric assessment.**

Vital Signs:

The following vital sign abnormality will **require discontinuation** if it is confirmed. Confirmation through re-testing should occur within 1 week:

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

Laboratory Abnormalities:

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

Laboratory Variable	Laboratory Value
Hematology	
Absolute Neutrophil Count	<1000/mm^3; <1.0 x10^9/L
Hemoglobin	<10.0 g/dL; <6.2 mmol/L; <100 g/L
Platelet count	<75,000/mm^3; <75.0x10^9/L
Lymphocytes	<500/mm3; <0.5x109/L
Chemistry	
AST[b]	>2.5x ULN
ALT	>2.5x 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

b. Additional investigations, such as review of ethanol, recreational drug and dietary supplement consumption should be done; testing for acute hepatitis A, B or C infection and biliary tract imaging should be promptly discussed with the Pfizer Medical Monitor or designee.

If an individual subject demonstrates CONCOMITANT serum creatinine-based AND serum 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 referral to nephrologist should be taken for evaluation and treatment as clinically indicated. Results should be repeated until eGFR returns to baseline ±15% (see protocol Section 8.4.3).

Other:

Pregnancy confirmed by serum β-hCG testing. Pfizer Medical Monitor or designee should be notified immediately.

Discontinuation/End of Treatment Monitoring for Adverse Events, Laboratory, and Vital Signs:

Any subject meeting discontinuation criteria must enter into the Follow up Period with their first follow up visit occurring 1 week after their last dose whenever possible, until the event has returned to normal or baseline levels or is deemed clinically stable. The procedures scheduled for Week 12 (end of treatment) Visit will be performed on the last day the subject takes the investigational product or as soon as possible thereafter. 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. 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.

Appendix 4. Prohibited Concomitant Medications

CYP3A4, 5, 7 Inhibitors	**CYP3A Inducers**	Strong P-gp inhibitors	Substrates of MDR1	Substrates of OCT2/MATE
HIV antivirals: -delavirdine (Rescriptor) -indinavir (Crixivan) -nelfinavir (Viracept) -ritonavir (Kaletra, Norvir) -saquinavir (Fortovase) amiodarone (Cordarone, Pacerone) cimetidine (Tagamet) ciprofloxacin (Cipro) clarithromycin (Biaxin, Prevpac) diethyl-dithiocarbamate diltiazem (Cardizem, Tiazac) fluconazole (Diflucan) fluvoxamine (Luvox) gestodene (Femodene, Melodene, Minulette, Mirelle, Triodene ED) grapefruit juice and marmalade itraconazole (Sporanox) ketoconazole (Nizoral) mifepristone (Mifeprex, RU486) nefazodone (Serzone) norfloxacin (Shibroxin, Noroxin) Norflouxetine Mibefradil verapamil (Calan SR,Covera HS, Isoptin SR, Tarka, Verelan)	barbiturates efavirenz (Sustiva) nevirapine (Viramune) barbiturates carbamazepine (Carbatrol, Tegretol) modafinil (Provigil) phenobarbital Phenytoin (Dilantin, Phenytek) rifampin (Rifadin, Rifamate, Rifater) St. John's wort troglitazone (Rezulin) pioglitazone (Actos) rifabutin (Mycobutin)	Quinidine	Digoxin	Dofetilide

Appendix 5. Columbia Suicide Severity Rating Scale (C-SSRS)[25]

C-SSRS for Screening and Baseline Visit

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

Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes No** ☐ ☐ Total # of Attempts ____	**Yes No** ☐ ☐ Total # of Attempts ____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes No** ☐ ☐	**Yes No** ☐ ☐

Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:			**Yes** ☐	**No** ☐	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:			**Yes** ☐	**No** ☐	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:			**Yes** ☐	**No** ☐	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?			**Yes** ☐	**No** ☐	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:		
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____		
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____		

[redacted]

CSSRS for any post-baseline visits

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

Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

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

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

[redacted]

Appendix 6. Suicidal Behaviors Questionnaire-Revised (SBQ-R)[26]

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 7. Patient Health Questionnaire – 8 items (PHQ-8)[27]

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 _____ = ___ + ___ + ___)

Appendix 8. Physician Global Assessment

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

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

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

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

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

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

CCI

CCI

[redacted]

[redacted]

CCI [redacted]

CCI [redacted]

[redacted]

CCI

[redacted]

[redacted]