A PHASE 2B, RANDOMIZED, DOUBLE BLIND, VEHICLE-CONTROLLED, PARALLEL-GROUP, DOSE RANGING STUDY TO ASSESS EFFICACY, SAFETY, TOLERABILITY AND PHARMACOKINETICS OF PF-06700841 TOPICAL CREAM APPLIED ONCE OR TWICE DAILY FOR 12 WEEKS IN PARTICIPANTS WITH MILD TO MODERATE CHRONIC PLAQUE PSORIASIS

Investigational Product Number:	PF-06700841
Investigational Product Name:	N/A
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	2018-003051-38
Protocol Number:	B7931023
Phase:	2b

Short Title: A PHASE 2B DOSE RANGING STUDY TO ASSESS EFFICACY, SAFETY, TOLERABILITY AND PHARMACOKINETICS OF PF-06700841 TOPICAL CREAM IN PARTICIPANTS WITH CHRONIC PLAQUE PSORIASIS

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**

Amendment 1	20 April 2020	This amendment is making the following substantial changes:
		
		• Addition of an option to add an additional cohort of participants in BID dosing arm (and corresponding vehicle arm) as Stage 2 of the study.
		
		  • Changes related to the optional, additional cohort are in the Protocol Summary (Section 1.1, Section 1.2, and Section 1.3), Objectives, Estimands, and Endpoints (Section 3), Study Design (Section 4.1, Section 4.2., and Section 4.3), Study Assessments and Procedures (Section 8.8 and Section 8.11), and Statistical Considerations (Section 9.2, Section 9.4, Section 9.5. and Section 9.6) sections.
		
		  Rationale: The addition of an additional arm is intended to allow more extensive exploration of the dose response of the PF-06700841 topical cream.
		
		This Amendment is making following non-substantial changes and some editorial changes:
		
		• Incorporation of all changes/clarifications to-date, made via Protocol Administrative Clarification letters (PACLs).
		
		  • Changes are in Protocol Summary (Section 1), Schedule of Activities (Section 1.3), Study population (Section 5.2 and Section 5.4), Study

		Assessments and Procedures (Section 8.2.1.2 and Section 8.2.2.3), and Interim Analysis (Section 9.5.1). • In the Protocol Summary (Section 1), Introduction (Section 2), and Study Design (Section 4) sections, changed text from "*The oral formulation of PF-06700841 has been studied in several trials, this is the first clinical study for its topical formulation in patients*" to "*The oral formulation of PF-06700841 has been studied in several trials, this is the first clinical study for its topical formulation in patients with mild to moderate plaque psoriasis*." **Rationale**: At the time of this Amendment, 2 other clinical studies (B7931029 and B7931022) evaluated topical formulation of PF-06700841 in its topical formulation (Section 2.2.2). • In the Protocol Summary (Section 1.1, and Section 1.3), Objectives and Endpoints (Section 3), Study Design (Section 4), and Study Assessments and Procedures (Section 8.8 and Section 8.11) sections, CCI [redacted] **Rationale**: As enrollment in Stage 2 will be limited to only 1 dosing arm and will have limited number of participants, ie, approximately 40, optional assessments will not be offered in Stage 2.

		• Updated Figure 1 and Table 2 to clarify the timing of Stage 2 in context of Stage 1 and to include additional arms (3% BID PF-06700841 and corresponding, BID vehicle arm). **Rationale**: Schematic updated to reflect the update in the study design. • Updated Clinical Overview Section (Section 2.2.2) to match the most current IB (September 2019) language; added newly started, completed and planned Phase 1 and Phase 2 studies using oral or topical formulations of PF-06700841. **Rationale**: Since the original protocol was issued, additional studies were completed, started or planned. Details were updated to match the updated Investigator's Brochure (September 2019). • Updated dose justification (Section 4.3) of newly added dosing arm in Stage 2. **Rationale:** As newly added dosing arm is of different strength compared to the ones being tested in Stage 1, justification of dose section is updated accordingly. • Updated participant Discontinuation/Withdrawal From the Study (Section 7.2) to highlight possible reasons of discontinuation or withdrawal from the study. **Rationale:** Discontuation or withdrawal reasons are updated to align with the data standards to be used in the study. • Updated Protocol Summary (Section 1.1) and Statistical Considerations (Section 9.2, Section 9.4, Section 9.5, and Section 9.6) sections to reflect changes made to the study design

		due to the additional cohort (in Stage 2). **Rationale**: As an additional dosing arm is being added, justification of number of participants selected for this Cohort is described. Interim analysis (Section 9.5) and PK/PD unblinding section (Section 9.6) are also updated accordingly. • Added QuantiFERON®-TB Gold Plus test as an acceptable IGRA assay in Study Assessments and Procedures (Section 8). **Rationale:** The assay, QuantiFERON®-TB Gold Plus test, was recently added to the list of acceptable IGRA assays by the central laboratory.
Original protocol	26 October 2018	Not applicable (N/A)

This amendment incorporates all revisions to date, including Protocol Administrative Clarification letters (PACLs), and amendments made at the request of country health authorities and IRBs/ECs.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A PHASE 2B, DOSE RANGING STUDY TO ASSESS EFFICACY, SAFETY, TOLERABILITY AND PHARMACOKINETICS OF PF-06700841 TOPICAL CREAM IN PARTICIPANTS WITH CHRONIC PLAQUE PSORIASIS

Rationale

This multicenter, randomized, double-blind, vehicle controlled, parallel group study is being conducted to provide data on efficacy, safety, tolerability and pharmacokinetics (PK) of PF-06700841 multiple topical formulation concentrations in mild to moderate plaque psoriasis. Additionally, the study is intended to enable selection of dose and dosing regimen (once daily, QD, vs twice daily, BID) for the future clinical development of topical PF-06700841. The oral formulation of PF-06700841 has been studied in several trials, this is the first clinical study for its topical formulation in patients with mild to moderate plaque psoriasis. The current nonclinical toxicology package supports the planned treatment duration of up to 13 weeks.

Objectives, Estimands, and Endpoints

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To compare the efficacy of multiple dose levels of PF-06700841 versus vehicle on change from baseline in psoriasis area and severity index (PASI) score in participants with mild to moderate plaque psoriasis.	• Change from baseline in PASI score at Week 12.	• Estimand E1: This estimand is intended to provide a population level estimate of the treatment effect of the investigational product (IP) alone on a continuous endpoint; without the benefit of additional prohibited medications, regardless of participants compliance with the IP dosing.
Secondary:	**Secondary:**	**Secondary:**
• To compare the efficacy of multiple dose levels of PF-06700841versus vehicle on physician global assessment (PGA) score in participants with mild to moderate plaque psoriasis.	Key secondary endpoint • Proportion of participants with PGA score clear (0) or almost clear (1) and ≥2 points improvement from baseline at Week 12.	• Estimand E2: This estimand is intended to provide a population level estimate of the treatment effect of the IP alone on a binary responder endpoint; without the benefit of additional prohibited medications, regardless of participants compliance with the IP dosing.
• To compare the efficacy of multiple dose levels of PF-06700841versus vehicle on the proportion of participants with mild to moderate plaque psoriasis achieving PASI 75.	• Proportion of participants achieving PASI 75 (75% or greater improvement from baseline) at time points specified in the SoA.	
• To compare the efficacy of multiple dose levels of PF-06700841 versus vehicle on	• Change from baseline and percent change from baseline in PASI scores at time points	• All other continuous secondary endpoints will be analyzed descriptively and using estimand

measures of disease and symptom severity in participants with mild to moderate plaque psoriasis.	specified in the SoA. • Absolute score and change from baseline in Peak-Pruritus Numerical Rating Scale score at time points specified in the SoA. • Absolute score and change from baseline Psoriasis Symptom Inventory at time points specified in the SoA. • Proportion of participants with PGA score clear (0) or almost clear (1) and ≥2 points improvement from baseline at time points specified in the SoA. • The proportion of participants who achieved a Psoriasis Symptom Inventory score of 0 (not at all) or 1 (mild) on every item at time points specified in the SoA.	E1 described above when appropriate. • All other categorical secondary endpoints will be analyzed descriptively and using estimand E2 described above when appropriate.
• To assess safety and tolerability of PF-06700841 in participants with mild to moderate plaque psoriasis.	• Incidence and severity of adverse events, serious adverse events and withdrawals due to adverse events. • Change from baseline in clinical laboratory values (chemistry, hematology and lipids). • Change from baseline in ECG parameters (heart rate, QT, QTc, PR and QRS intervals). • Change from baseline in vital signs (blood pressure, pulse rate and temperature measurements). • Incidence of severity grades in skin tolerability at times indicated in SoA.	• There is no defined estimand for these endpoints and they will be analyzed using Pfizer data standards as applicable.

Overall Design

This is a Phase 2b, randomized, double-blind, vehicle-controlled, parallel group, multicenter study in participants with mild to moderate plaque psoriasis. The study will be conducted in 2 stages where an additional cohort (Stage 2) of participants may be added, following completion of enrollment into Stage 1 and at the discretion of the Sponsor. Investigators, study participants, and Pfizer study team members will remain blinded to results of Stage 1.

In addition, this study will use an internal review committee (IRC) for ongoing monitoring of safety and efficacy of participants in the study according to the IRC charter.

CCI [redacted]

Number of Participants

In Stage 1, approximately 240 participants are planned to be randomized into the study to allow for approximately 192 evaluable participants (approximately 24 completers per arm, 8 arms). See Section 9.2 for details. Participants will be randomized to 1 of 8 treatment groups in QD (4 active and 1 vehicle) or BID (2 active and 1 vehicle) dosing regimen in the ratio of 1:1:1:1:1:1:1:1.

In Stage 2, approximately 40 participants are planned to be randomized to allow for approximately 32 evaluable participants. Participants will be randomized into 1 of 2 treatment groups in BID (1 active and 1 vehicle) dosing regimen, in the ratio 3:1.

The eligibility criteria for participants enrolled in Stage 1 and Stage 2 are the same.

A study schematic with treatment arms is shown in Section 1.2.

CCI [redacted]

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to the investigational product/entered in the study.

All participants randomly assigned to the investigational product (IP) and who apply at least 1 dose of IP will be analyzed according to the product they actually received. For participants who discontinue treatment and/or receive prohibited medication, efficacy data (eg primary and key secondary endpoints) will be censored starting at the ET visit.

Intervention Groups and Duration

Once a participant is enrolled, the study duration will be approximately 22 weeks, including up to a 6 week screening period, 12 week treatment period, and approximately 4 week follow up period in both Stage 1 and Stage 2. Treatment groups are shown in the table below. Vehicle cream contains all excipients as the PF-06700841 cream except for PF-06700841 (See Section 6.1).

Stage	Treatment Group	Investigational Product
1	A	Vehicle cream QD
	B	PF-06700841 0.1% cream QD
	C	PF-06700841 0.3% cream QD
	D	PF-06700841 1.0% cream QD
	E	PF-06700841 3.0% cream QD
	F	Vehicle cream BID
	G	PF-06700841 0.3% cream BID
	H	PF-06700841 1.0% cream BID
2	I	PF-06700841 3.0% cream BID
	J	Vehicle cream BID

The IP application regimen should not be modified. Temporary discontinuation and/or permanent discontinuation of the IP may be appropriate under some circumstances (See Section 7.1.1).

Data Monitoring Committee: Yes

This study will use an internal review committee (IRC) to perform safety and efficacy analysis for making internal business decisions. The details of the objectives, decision criteria, dissemination plan and method of maintaining the study blind will be documented in the IRC charter for any analysis that committee is asked to perform. Members of the IRC will be qualified and experienced in reviewing and interpreting clinical study data. They will be independent of the study team, and unblinded to treatment.

In addition, an interim analysis will be conducted at the end of Stage 1. Some Pfizer team members and other key stakeholders will become unblinded to the results of Stage 1. Unblinded Pfizer team members will be replaced by blinded team members. Investigators and study participants will remain blinded to the results of Stage 1.

An external blinded adjudication committee will be selected on ad-hoc basis, if suspected cardiovascular and/or thromboembolic (TE) events are observed during study conduct. Other safety events for adjudication may be identified and included in the remit of the safety adjudication committee as appropriate.

Statistical Methods

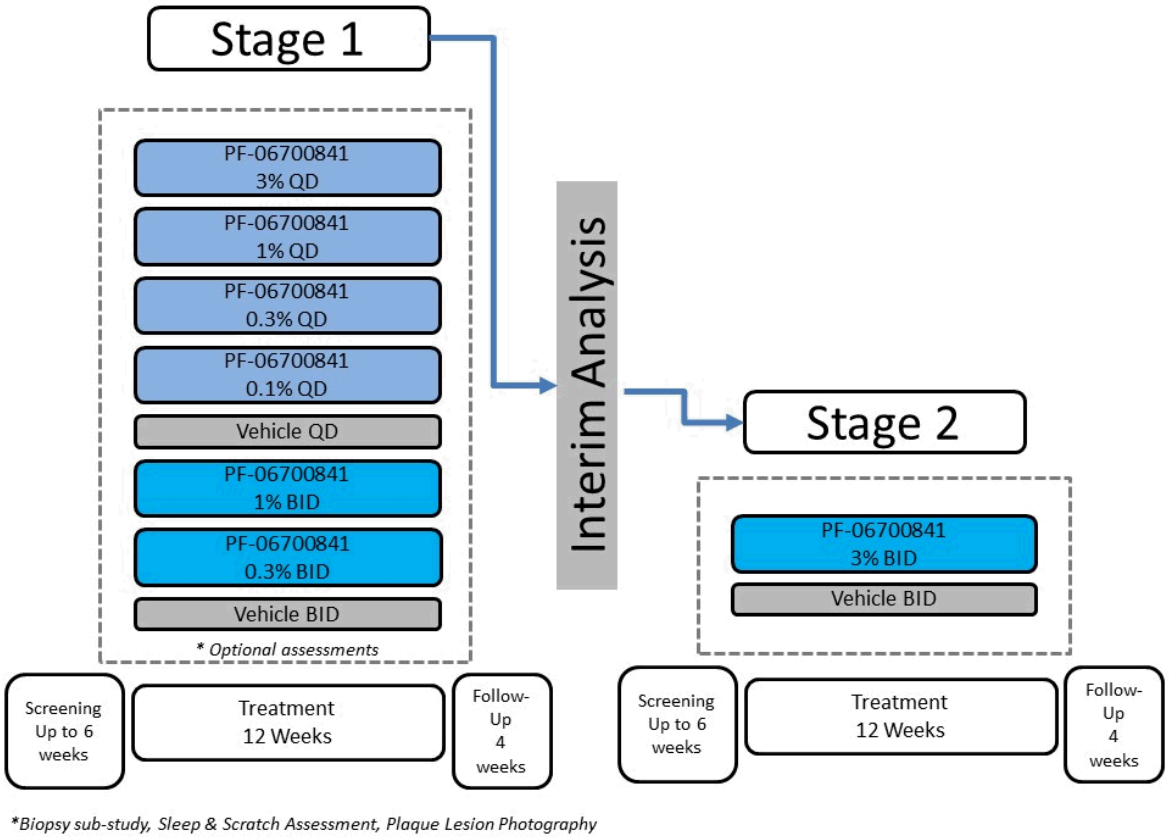
The primary estimand will be the population average treatment effect on change from baseline in PASI (psoriasis area and severity index) scores at Week 12 relative to vehicle (with the same dosing schedule, QD or BID) without regard to compliance in the absence of prohibited medication. Measurements after the initiation of prohibited medication will be censored and treated as missing data.

The secondary estimand will be the population average treatment effect on the PGA (Physician Global Assessment) response rate: percentage of participants with a score of clear (0) or almost clear (1) and ≥2 point improvement from baseline at Week 12 relative to vehicle (with the same dosing schedule, QD or BID) without regard to compliance with IP in the absence of prohibited medication.

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

The sample size is based on the primary efficacy endpoint, PASI change from baseline at Week 12.

1.2. Schema



*Biopsy sub-study, Sleep & Scratch Assessment, Plaque Lesion Photography

1.3. Schedule of Activities (SoA)

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

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

Schedule of Activities

Visit Identifier[a]	Screening	Day 1[u]	Week 1[u]	Week 2[u]	Week 4[u]	Week 6[u]	Week 8[u]	Week 10[u]	Week12/ ET[b,u]	Week 14 Follow-up[u]	Week 16 Follow-up/ET[b,u]
Visit Day/Window[a]	**Day -42 to -1**	**Day 1**	**Day 8 ±1 day**	**Day 15 ±2 days**	**Day 29 ±2 days**	**Day 43 ±2 days**	**Day 57 ±2 days**	**Day 71 ±2 days**	**Day 85 ±2 days**	**Day 100 ±3 days**	**Day 118 ±3 days**
Enrollment Procedures											
Informed consent	X										
Eligibility assessment	X	X									
Medical history	X										
Medication history	X										
Demography	X										
Randomization		X									
Clinical assessments											
Full physical examination	X	X							X		
Brief physical examination			X	X	X	X	X	X			X
Vital signs	X	X				X			X		
Weight	X	X							X		X
Height	X										
ECG[c]	X	X				X			X		
Chest radiograph[d]	X										
C-SSRS	X										
Local tolerability assessment		X	X	X	X	X	X	X	X	X	X
Clinical assessments of psoriasis											
PASI	X	X	X	X	X	X	X	X	X	X	X
CCI											
PGA	X	X	X	X	X	X	X	X	X	X	X

Visit Identifier[a]	Screening	Day 1[u]	Week 1[u]	Week 2[u]	Week 4[u]	Week 6[u]	Week 8[u]	Week 10[u]	Week12/ ET[b,u]	Week 14 Follow-up[u]	Week 16 Follow-up/ET[b,u]
Visit Day/Window[a]	**Day -42 to -1**	**Day 1**	**Day 8 ±1 day**	**Day 15 ±2 days**	**Day 29 ±2 days**	**Day 43 ±2 days**	**Day 57 ±2 days**	**Day 71 ±2 days**	**Day 85 ±2 days**	**Day 100 ±3 days**	**Day 118 ±3 days**
Laboratory samples											
Safety labs (Hematology, Blood chemistry, Urinalysis)[e]	X	X	X	X	X	X	X	X	X	X	X
Lipid panel (Fasting)[e]		X							X		
Serum cystatin C[e]		X	X	X	X	X	X	X	X	X	X
Blood pregnancy test[f]	X	X									
Urine pregnancy test[e,f]		X	X	X	X	X	X	X	X	X	X
FSH[g]	X										
Hepatitis tests	X								X[h]		
HIV test	X										
Tuberculosis test[i]	X										
CCI											
IP-related											
CCI											
Identify treatment eligible psoriasis areas[l]	X	X									
Provide treatment area list to study participant		X									
Review and update (as needed) treatment area list[m]			X	X	X	X	X	X			
Dispensing of IP		X	X	X	X	X	X	X			
IP application, observation[n]		X	X	X	X	X	X	X	X[o]		
Collect and Weigh Previous IP Tubes (prior to dispensing new IP)			X	X	X	X	X	X	X		
Training on and dispensing dosing e-diary/ePRO device		X									
Filling in dosing e-diary		X	→	→	→	→	→	→	X		
Dosing e-diary review and re-training as needed		X	X	X	X	X	X	X	X		
Collecting e-diary/ePRO device											X

Visit Identifier[a]	Screening	Day 1[u]	Week 1[u]	Week 2[u]	Week 4[u]	Week 6[u]	Week 8[u]	Week 10[u]	Week12/ ET[b,u]	Week 14 Follow-up[u]	Week 16 Follow-up/ET[b,u]
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Monitoring											
Contraception check[p]	X	X	X	X	X	X	X	X	X	X	X
Concomitant Treatment(s)		X	→	→	→	→	→	→	→	→	X
Serious and non-serious adverse event monitoring	X	→	→	→	→	→	→	→	→	→	X
Patient Reported Outcomes[q]											
Psoriasis Symptom Inventory[r]		X	→	X	X	X	X	X	X	X	X
Peak-Pruritus Numerical Rating Scale[r]		X	→	X	X	X	X	X	X	X	X
CCI											
Training on ePRO device		X									
Review of ePRO entries		X	X	X	X	X	X	X	X		
CCI											

Abbreviations: → = ongoing/continuous event; CCI ; C-SSRS= Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; ePRO = Electronic patient reported outcomes; ET = Early Termination; FSH= follicle stimulating hormone; HIV= human immunodeficiency virus; CCI IP = Investigational Product; CCI ; PASI = Psoriasis Area and Severity Index; PGA= Physician's Global Assessment; CCI ; PRO = patient reported outcome; CCI

a. Day relative to start of study treatment (Day 1).

b. For participants who discontinue from the study prior to Week 12 visit, the procedures scheduled for Week 12 will be performed as soon as possible. Whenever possible, these participants should have one visit approx. two weeks after the last dose (Week 14 Follow up visit assessments) and the last visit at least 28 days after the last dose of IP was administered (Week 16 Follow-up visit assessments). For participants who discontinue from the study after Week 12 visit, the procedures scheduled for Week 16 will be performed.

c. Local read, single ECG at all scheduled time points. Triplicate ECG will be conducted as appropriate as described in Section 8.2.2.4.

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

e. Participants must be fasting (water only) for at least 8 hours prior to visits, when lipid panel is being taken. Lipid panel includes total cholesterol, LDL, HDL, triglycerides. Protocol-specified safety laboratory tests may be performed at a local laboratory, where allowable by law or local guidance, if the study participant is unable to visit the study site. Local laboratory reference ranges and a copy of local lab results should be included in participant's source documents.

f. Required for female participants of childbearing potential. Pregnancy tests (serum/urine) may also be repeated more frequently as per request of IRBs/ECs or if required by local regulations. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Two negative pregnancy tests are required before receiving IP (one negative serum pregnancy test at screening and one negative urine pregnancy test at Day 1 visit). If urine pregnancy test is positive after IP application, serum pregnancy test will be conducted, IP paused and sponsor clinician and sponsor medical monitor notified immediately (See Section 7.1.1).

g. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). See Section 10.4.3.

h. In Japan only: HBV DNA reflex test. See Sections 10.2 and 10.8.

i. If performed within 12 weeks prior to Day 1 and documentation is available, this does not have to performed during Screening.

C
C
I [redacted]

l. Potential treatment area(s) will be identified at Screening, and final selection will be made at Day 1.

m. If participants develop new treatment areas after Day 1 between clinic visits, participants should contact the Investigator and determine if these may be eligible for treatment as described in Section 6.1.1.1. This may result in an additional unscheduled visit and dispensing of IP.

n. Except for Day 1, participants will apply IP after all assessments have been completed. Participants will also apply IP in between visits. For BID dosing regimen, only one dose will be observed in the clinic.

o. Last dose for both BID and QD dosing will be applied either prior to or during the Week 12 clinic visit. Participants on both dosing regimen will receive only one dose on their last day. IP application will not be performed during early termination visit.

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

q. Every effort should be made for the participant to complete all patient reported outcome (PRO) questionnaires before any other assessments.

C
C [redacted]

t. Participants who consent to these optional assessments, may be trained on and have devices issued after participant eligibility has been confirmed. This will be part of Screening but may take place at a different in-clinic visit no later than 1 week prior to Day 1. See Section 8.11.2 for details on how long devices should be worn.

u. In the event that any in-clinic study visit cannot be conducted, including scheduled follow-up visit, the participant site visits may be changed to phone calls or video visits (if permitted by law or local guidance) to reduce risk of potential participant exposure to COVID-19.

2. INTRODUCTION

PF-06700841 is a dual inhibitor of human tyrosine-protein kinase 2 (TYK2) and Janus kinase 1 (JAK1) that is currently being investigated in participants with multiple indications. The oral formulation of this compound has been studied in several studies, including in patients with psoriasis. This study is the first study for the topical formulation of PF-06700841 in patients with mild to moderate plaque psoriasis.

2.1. Study Rationale

The purpose of this multicenter, randomized, double-blind, vehicle controlled, parallel group study is to determine efficacy, safety, tolerability and pharmacokinetics of PF-06700841 in its topical formulation in participants with mild to moderate psoriasis. In addition, data from this study will be used to select a topical dose and dosing regimen (once daily vs. twice daily application) for the future clinical development of PF-06700841. Oral formulation of PF-06700841 has been studied in several trials, this is the first clinical study for its topical formulation in patients with mild to moderate plaque psoriasis.

2.2. Background

The most common variant of psoriasis, plaque psoriasis, is a chronic inflammatory skin disease characterized by red, scaly, raised plaques. Chronic plaque psoriasis is a common skin disorder with a worldwide prevalence of 2% and afflicts an estimated 5.8-7.5 million Americans.[1] Although psoriasis primarily affects the skin and is not a life-threatening disease, it can profoundly impact the patient's quality of life (QoL) resulting in an impairment akin to other major diseases, such as type 2 diabetes, myocardial infarction, and arthritis.[2]

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.[3,4] 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 are expected to 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.[5,6]

Increased activation of Th17 and the main effector cytokines of Th17 cells has been linked to various inflammatory diseases, including psoriasis.[7] The number of Th17 cells are elevated in psoriatic lesions, along with levels of proinflammatory cytokines, including IL-17A and IL-17F, which are expressed by Th17 cells and are likely mediators of inflammation and tissue damage.[7,8] Human genetic studies implicate the Th17 pathway in psoriasis, and have uncovered likely risk alleles which include genes involved in IL-23 signaling (including TYK2, which mediates IL-23 receptor signaling) and genes that function downstream of the IL-17 receptor.[7]

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 and ixekizumab selectively target IL-17A and have been shown to be effective in the treatment of psoriasis.[9] Other therapies such as cyclosporine, phototherapy, and infliximab also inhibit the IL-17 pathway.[10-12] The monoclonal antibodies ustekinumab and guselkumab, which are also effective in treating psoriasis,[13-15] disrupt IL-23 activation of Th17 cells.[16] Thus, there is strong rationale for targeting the Th17 pathway in the treatment of psoriasis.

In the skin, cytokines mediated by JAK signaling impact several cellular inflammatory functions, such as apoptosis of inflammatory T cell infiltrates and T helper cell differentiation. C-X-C motif chemokine ligand 10 (CXCL10), chemokine ligand 26 (CCL26) and matrix metallopeptidase (MMP12) have been reported to be induced by cytokines acting via the JAK class of kinases[17-20] and are implicated in inflammatory and autoimmune conditions of the skin.[21-26] In addition, impairment of the skin barrier protein filaggrin has also been implicated in inflammatory and autoimmune diseases of the skin[27] and its expression has been reported to increase upon inhibition of JAK enzymes.[20] Following topical application of the clinical formulation to freshly excised human skin, PF-06700841 caused a dose-dependent inhibition of gene expression of pro-inflammatory molecules CXCL10, CCL26 and MMP12 (measured by changes in messenger ribonucleic acid [mRNA] in the presence and absence of PF-06700841) and a dose-dependent stimulation of the skin barrier protein, filaggrin. Thus, PF-06700841 showed pharmacological modulation in human skin by the topical application, consistent with the known activity of PF-06700841 on JAK1 and TYK2 enzymes.

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, thereby providing therapeutic benefit in the treatment of plaque psoriasis.

2.2.1. Non-Clinical Experience of PF-06700841

CCI [redacted]

CCI [redacted]

Further details are provided in the current Investigator's Brochure.

2.2.1.2. Non-Clinical Safety Studies

No adverse findings were observed in a 13-week dermal repeat-dose toxicity study with PF-06700841 in minipigs. PF-06700841-related nonadverse target organs identified from topical application included the skin (erythema, edema, eschar) and the immune and hematolymphopoietic systems (thymus and peripheral blood). In addition, vehicle-related nonadverse erythema and edema were observed. The findings in the thymus (lower weights without correlating microscopic changes) and peripheral blood (decreased lymphocytes) are consistent with the pharmacological activity of PF-06700841. PF-06700841 was negative for skin sensitization potential in the mouse local lymph node assay when applied topically as a solution (up to 50%) or cream formulation (3%). The no-observed-adverse-effect-level (NOAEL) in the 13-week dermal toxicity study for PF-06700841 by topical administration was the highest dose of 1.28 mg/cm^2/day (3% cream formulation), resulting in systemic mean unbound C_{max} and AUC_{24} exposures of 108 ng/mL and 1760 ng•h/mL, respectively.

No adverse findings were observed in oral repeat-dose toxicity studies with PF-06700841 in rats and monkeys up to 6 and 9 months in duration, respectively. PF-06700841-related, nonadverse, target organs identified include the immune and hematolymphopoietic systems (thymus, spleen, lymph nodes, and bone marrow), cardiovascular system (blood pressure, heart rate, QTc interval), 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. The NOAELs in the 6-and 9-month toxicity studies were 45 mg/kg/day in rats (unbound C_{max} of 8280 ng/mL and AUC_{24} of 69,700 ng•h/mL) and 20 mg/kg/day in monkeys (unbound C_{max} of 2260 ng/mL and AUC_{24} of 10,700 ng•h/mL). Adverse findings in the central nervous system (decreased activity, mortality, prostration, convulsions) were observed at high systemic exposures in pregnant, but not in nonpregnant rabbits.

In oral embryo-fetal development studies in rats and rabbits, adverse PF-06700841-related developmental effects occurred (lower embryo-fetal viability and mean fetal body weights, fetal skeletal malformations, external malformations). The developmental NOAEL in rabbits was 1 mg/kg/day (unbound C_{max} of 174 ng/mL and AUC_{24} of 608 ng•h/mL). The developmental NOAEL in rats was not established and is <2 mg/kg/day (unbound C_{max} of 482 ng/mL and AUC_{24} of 2240 ng•h/mL), the lowest dose tested. No effects on female reproductive organs, as assessed by histopathologic examination, were noted in either the rat or monkey repeat-dose toxicity studies. PF-06700841 is not mutagenic in bacterial reverse mutation assays. Although PF-06700841 was positive for micronuclei formation in vitro (through an aneugenic mechanism), it did not induce micronuclei in vivo in rats at 55 mg/kg/day (unbound C_{max} = 7730 ng/mL and AUC_{24} = 88,300 ng•h/mL), the highest dose

tested in the 1-month oral toxicity study. No evidence of PF-06700841-related phototoxicity in the skin or eyes of pigmented rats in a 3-day oral phototoxicity study was observed up to the highest dose tested of 100 mg/kg/day, demonstrating that PF-06700841 was not a phototoxicant, in vivo.

Further details of the nonclinical safety program are provided in the current Investigator's Brochure.

2.2.2. Clinical Overview

To date, the clinical development program for PF-06700841 comprises Phase 1 studies in adult healthy Western participants (B7931001; single ascending dose [SAD] and multiple ascending dose [MAD] study, B7931010; PK profile and relative bioavailability study, B7931014 (ongoing); an absorption, distribution, metabolism and excretion of [^{14}C PF-06700841] study, B7931019 (ongoing); effect on QTc interval study, and B7931033 (planned); studying the effect of multiple oral doses of itraconazole on a single oral dose of PF-06700841 PK study) and in Japanese participants (B7931009; placebo-controlled multi-dose study and B7931029; vehicle and white petrolatum-controlled study to assess skin irritation potential study), and Phase 1 and 2 studies in participants with chronic plaque psoriasis (B7931001, B7931004), alopecia areata (B7931005), atopic dermatitis (B7931022), systemic lupus erythematosus (B7931028), psoriatic arthritis (B7931030), ulcerative colitis (B7981005), Crohn's disease (B7981007), vitiligo (B7981019), and hidradenitis suppurativa (C2501007; ongoing). The studies conducted to date described in this section have all used oral administration of PF-06700841, except for B7931022 (ongoing) and B7931029 (completed) which used multiple dose strengths of topical cream formulation of PF-06700841 in participants with mild-to-moderate atopic dermatitis and healthy Japanese participants, respectively.

As of the latest update to the Investigator's Brochure (IB, September, 2019), PF-06700841 was generally safe and well tolerated in healthy participants (B7931001 and B7931009); psoriasis (B7931001 and B7931004) and alopecia areata participants (B7931005). There were no clinically meaningful findings in vital signs, ECG, suicidal behavior or ideation, or potential Hy's Law cases reported during these studies. A summary is provided below, further details are provided in the current Investigator's Brochure (September 2019).

Table 1. PF-06700841 Clinical Development Program – Completed, Ongoing, and Planned Studies as of September 2019 IB

Study ID	Description	PF-06700841 Dose/Regimen	# of Participants
Phase 1 Studies:			
B7931001 (completed)	The study consisted of 3 parts: 1. Within Cohort, randomized, double-blind, placebo-controlled, single and multiple dose escalation, parallel group to assess safety, tolerability, PK, and PD of PF-06700841 in healthy adult Western participants.	SAD: 1, 3, 10, 30, 100, and 200 mg; MAD: 10, 30, 100, or 175 mg QD or 50 mg BID[a] for 10 days	54 (8/cohort) (6 active: 2 placebo)
	2. Randomized, placebo-controlled, 4-week treatment period in adult participants with PsO to assess PF-06700841 safety, tolerability and effect on disease activity measured by PASI.	Placebo, 30, or 100 mg QD for 28 days	30 (9 placebo; 14 at 30 mg QD; 7 at 100 mg QD)
	3. Bioavailability assessment of a tablet formulation relative to suspension formulation and the effect of food on a tablet formulation of PF-06700841.	Single dose: 100 mg in a 3-way cross-over design	12
B7931009 (completed)	Randomized, double-blind, placebo-controlled, multiple dose study in healthy Japanese adult participants.	100 mg QD for 10 days	8 (6 active: 2 placebo)
B7931010 (Completed)	An open-label, single dose, 2-period, 2-sequence crossover study in healthy volunteers to characterize PF-06700841 PK profile and relative bioavailability following single oral dose formulation of IR tablets and MR tablets.	Sequence 1: a single oral dose of 30 mg PF-06700841 IR tablets to a single oral dose of 30 mg PF-06700841 MR tablets Sequence 2: a single oral dose of 30 mg PF-06700841 MR tablets to a single oral dose of 30 mg PF-06700841 IR tablets	8 enrolled and completed
B7931014 (Ongoing)	A Phase 1, open label, non-randomized, 2 period, fixed sequence study to investigate the absorption, distribution, metabolism and excretion of [^{14}C PF-06700841] and to assess the absolute bioavailability and fraction absorbed of PF-06700841 in healthy male participants using a ^{14}C microtracer approach.	Period A: an oral dose of 60 mg PF-06700841 containing 300 nCi ^{14}C-PF-06700841; Period B: an oral dose of 60 mg unlabeled PF-06700841 followed by an IV dose of 30 µg ^{14}C labeled PF-06700841 (300 nCi)	6 enrolled and completed

Table 1. PF-06700841 Clinical Development Program – Completed, Ongoing, and Planned Studies as of September 2019 IB

Study ID	Description	PF-06700841 Dose/Regimen	# of Participants
B7931019 (Ongoing)	Phase 1, 6-sequence, 3-period, participant and investigator blinded and sponsor-open, crossover study in healthy volunteers to evaluate the PF-06700841 effect on QTc interval. Each participant randomized will receive placebo, PF-06700841 200 mg and moxifloxacin (open label) in one of the 6 sequences. Moxifloxacin is positive control to demonstrate the study sensitivity and PF-06700841 effect on QTc will be assessed by concentration-QT analysis.	Sequence 1: single dose of PF-06700841 200 mg to placebo to moxifloxacin 400 mg Sequence 2: single dose of PF-06700841 200 mg to moxifloxacin 400 mg to placebo Sequence 3: placebo to PF-06700841 200 mg to moxifloxacin 400 mg Sequence 4: placebo to moxifloxacin 400 mg to PF-06700841 200 mg Sequence 5: moxifloxacin 400 mg to PF-06700841 200 mg to placebo Sequence 6: moxifloxacin 400 mg to placebo to PF-06700841 200 mg	33 enrolled 32 completed
B7931029 (Completed)	A Phase 1, single center, randomized, vehicle and white petrolatum-controlled, evaluator blinded study to assess the skin irritation potential with a range of concentrations of PF-06700841 cream including vehicle and empty patch with white petrolatum under occlusive conditions in adult Japanese healthy participants.	PF- 06700841 cream 0% [vehicle], 0.1%, 0.3%, 1%, 3%, and empty patch with white petrolatum)	20 participants enrolled and completed
B7931033 (Planned)	A Phase 1, open-label, fixed-sequence, 2-period study to investigate the effect of multiple oral doses of itraconazole on a single oral dose of PF-06700841 PK in healthy volunteers.	Period 1: a single oral dose of 30 mg PF-06700841 tablets Period 2: Itraconazole 200 mg once daily on Days 1-7 with a single oral dose of 30 mg PF-06700841 tablets administered approximately 1 hour after itraconazole dosing on Day 4	12 Planned
Phase 2 Studies:			
B7931004 (completed)	A Phase 2a, randomized, double-blind, placebo-controlled study to evaluate safety and efficacy of PF-06700841 in participants with moderate to severe plaque psoriasis. The study consisted of 4 weeks of induction and 8 weeks of maintenance therapy periods.	Placebo, PF-06700841: 60 mg QD to 30 mg QD 60 mg QD to 10 mg QD 60 mg QD to 100 mg QW 60 mg QD to placebo 30 mg QD	212 (189 active and 23 placebo)

Table 1. PF-06700841 Clinical Development Program – Completed, Ongoing, and Planned Studies as of September 2019 IB

Study ID	Description	PF-06700841 Dose/Regimen	# of Participants
B7931005[b] (ongoing)	Phase 2a randomized, double-blind, placebo-controlled, multicenter study with two extension periods to evaluate the efficacy and safety profile of PF-06651600 and PF-06700841 in participants with moderate to severe AA. This includes a 24-week treatment period, a 4-week drug holiday (#1), an up to 12 month single-blind extension period, a 4-week drug holiday (#2), and a 6-month cross-over open label extension Period.	PF-06700841: 60 mg QD in 4-week induction and 30 mg QD in 20-week maintenance or placebo	142 enrolled (47 on active PF-06700841 and 47 on placebo)/ 115 completed (36 on active PF-06700841 and 34 on placebo) In extension 1, 96 participants entered single-blind extension (SBE) period, 32 received PF-06700841 and 25 completed the study In extension 2, 23 participants entered cross-over (CO) extension period and 5 participants received PF-06700841
B7931022 (Ongoing)	A Phase 2B, randomized, double blind, vehicle controlled, parallel group, dose ranging study to assess the efficacy, safety, tolerability and pharmacokinetics of PF-06700841 cream applied once or twice daily for 6 weeks in participants with mild or moderate atopic dermatitis.	PF-06700841 (topical) 0.1% 0.3% 1% 3% Vehicle	32 randomized (out of 280 planned) (as of 22-Aug-2019)
B7931028 (Ongoing)	A randomized, controlled, double-blinded study to evaluate the efficacy and safety of 3 doses of PF-06700841 compared to placebo in patients with active systemic lupus erythematosus receiving concomitant standard of care therapy.	PF-06700841 15 mg/day oral PF-06700841 30 mg/day oral PF-06700841 45 mg/day oral Placebo	46 enrolled (as of 12 Aug 2019)

Table 1. PF-06700841 Clinical Development Program – Completed, Ongoing, and Planned Studies as of September 2019 IB

Study ID	Description	PF-06700841 Dose/Regimen	# of Participants
B7931030 (Ongoing)	A Phase 2B, randomized, double-blind, placebo-controlled, dose-range,parallel group study of PF-06700841 to evaluate the efficacy of PF-06700841 at 16 weeks and to evaluate the safety and efficacy up to 1 year in participants with active psoriatic arthritis.	PF-06700841 60 mg QD, 30 mg QD, and 10 mg QD or placebo	3 enrolled (out of 196 planned) (as of 22-Aug-2019)
B7981005[b] (ongoing)	Double-blind, randomized, placebo-controlled, parallel group, multi-center dose-ranging study of oral PF-06651600 and PF-06700841 as induction and chronic therapy in participants with moderate to severe ulcerative colitis. The study has 8-weeks of double-blind and placebo-controlled induction treatment period followed by a 24-week of chronic active treatment period.	Induction treatment period: PF-06700841 60 mg QD, 30 mg QD, and 10 mg QD or placebo Chronic treatment period: PF-06700841 30 mg QD	216 enrolled (360 planned 71 completed (as of 09 Sep 2019)
B7981007[b] (ongoing)	Double-blind, randomized, placebo-controlled, parallel group study to evaluate the efficacy and safety of oral PF-06651600 and PF-06700841 as induction and open label extension treatment in participants with moderate to severe Crohn's disease (CD). The study has a 12-week induction treatment period followed by a 52-week open label active treatment period.	Induction treatment period: PF-06700841 60 mg QD or placebo Extended open label active treatment period: PF-06700841 30 mg QD	73 enrolled/250 planned 2 completed (as of 12 Sep 2019)
B7981019[b] **Ongoing**	A Phase 2b randomized, double-blind, placebo-controlled, multicenter, dose-ranging study to evaluate the efficacy and safety profile of PF-06651600 with a partially blinded extension period to evaluate the efficacy and safety of PF-06651600 and PF-06700841 in participants with active non-segmental vitiligo. The study has a 4-week induction, 20-week maintenance with PF-06651600. After the 4-week of drug holiday, participants may receive	During extension treatment period: PF-06700841 60 mg QD (4 weeks) to 30 mg QD (16 weeks)	1(enrolled)/60 (planned) as of 11 Sep 2019

Table 1. PF-06700841 Clinical Development Program – Completed, Ongoing, and Planned Studies as of September 2019 IB

Study ID	Description	PF-06700841 Dose/Regimen	# of Participants
	PF-06700841 during extended treatment period.		
C2501007 Planned	A planned Phase 2a, multicenter, randomized, double blind placebo-controlled, 16-week study evaluating the safety and efficacy of IRAK4 inhibitor PF-06650833, TYK2/JAK1 inhibitor PF-06700841, Tyk2 inhibitor PF-06826647 in adult with moderate to severe hidradenitis suppurativa (HS).	PF-06700841 45 mg QD	192 (Planned)

AA = Alopecia areata; BID = Twice daily; CD = Crohn's disease; IRAK4 = interleukin-1 receptor-associated kinase 4; MAD = multiple ascending dose; PASI = Psoriasis Area and Severity Index; PD = pharmacodynamic; PK = Pharmacokinetic; Mg = milligram; PsO = Psoriasis; QD = Once daily; QW = Once weekly; SAD = Single ascending dose; UC = Ulcerative colitis.

a. Participants who completed the 100 mg SAD and 100 mg MAD periods continued in the 50 mg BID period and received either placebo or PF-06700841 twice daily according to original treatment assignment when randomized into the 100 mg SAD period.

b. Platform study that will assess efficacy and safety of PF-06700841 and a second investigational agent (PF-06651600) separately. PF-06651600 is an orally bioavailable small molecule that irreversibly inhibits JAK3.

2.2.2.1. Study B7931001

In B7931001 study, the most commonly reported all causality TEAEs across active healthy participants were blood creatinine increased, reported in 2 participants during the SAD (single ascending dose) period and 11 participants during the MAD (multiple ascending dose) period, without any changes in Cystatin C measured renal function. Neutropenia was reported in four participants during the MAD period, most of them were mild in severity except one with moderate, and none of them reached <500/mm^3 during the study. The most frequently observed laboratory abnormalities in healthy participants were elevated LDL and serum creatinine. There were no deaths or SAEs reported in the Phase 1 studies. One psoriasis participant receiving 100 mg QD of IP in B7931001 experienced an adverse event of herpes zoster during the follow up period, after completing 28-day treatment.

2.2.2.2. Study B7931009

PF-06700841 demonstrated acceptable safety and tolerability by oral administration in study B7931009, which included 8 Japanese participants who were treated and completed the study. Six (6) participants received the treatment of PF-06700841 100 mg QD and 2 participants received matching placebo orally for 10 days.

2.2.2.3. Study B7931004

A total of 189 psoriasis participants out of 212 enrolled in B7931004 were exposed to at least one dose of PF-06700841 during the study. The proportion of participants with all-causality treatment-emergent adverse events (TEAEs) was comparable across all treatment groups but numerically higher in the active treatment groups (64.0% to 76.7%) than the placebo group (56.5%). The majority of participants in all treatment groups experienced mild or moderate all-causality TEAEs, and only 5.2% experienced severe all-causality TEAEs. Overall, there were no dose dependent increases in the all-causality TEAEs. Most TEAEs in the Infection and Infestation were mild to moderate except one participant who had two serious infections after taking a single dose of 60 mg PF-06700841 on Day 1. One participant in the 30 mg QD to 100 mg QW group had squamous cell carcinoma of skin reported on Day 2 of treatment. One participant in the 30 to 10 mg group was confirmed to be pregnant after in the study 42 days and discontinued from the study with obstetrical ultrasound demonstrating fetal cleft lip.

Decreased reticulocytes, hemoglobin, and neutrophils were observed in the participants on active treatment during 4-week induction phase and returned toward baseline level during 8-week maintenance phase. Increases in serum creatinine from baseline were observed in all active treatment groups with no association of change in cystatin C based renal function measurement. Other commonly reported laboratory abnormalities were elevation of low density lipoprotein (LDL) with no clinical meaningful changes in LDL/high-density lipoprotein (HDL) ratio. There were no clinically meaningful changes from baseline observed in creatine kinase (CK) during the study. CK levels >10 × upper limit of normal (ULN) were observed in two participants without adverse event. One moderate AE of CK-MB increased reported by one participant in the 30 to 10 mg QD group during the induction period, which was considered to be related to the IP by the investigator. No participant was discontinued from the study due to CK elevation.

2.2.2.4. Ongoing Phase 2 Studies

Oral PF-06700841 is currently being investigated in several studies: alopecia areata (B7931005), ulcerative colitis (B7981005), atopic dermatitis (B7931022), psoriatic arthritis (B7931030), vitiligo (B7981019), systemic lupus erythematosus (B7931028), Hidradenitis Suppurativa (C2501007), and Crohn's disease (B7981007). B7931005 study results from interim CSR are included below.

2.2.2.4.1. Study B7931005

47 alopecia areata participants were exposed to at least one dose of PF-06700841 in the B7931005 study. CCI [redacted]

CCI [redacted]

2.2.3. Overview of Clinical Pharmacology

2.2.3.1. Study B7931001

Following single oral doses of PF-06700841, peak plasma concentrations generally occurred at or before 1 hour for doses of 1 mg to 200 mg. In general, both AUC_{inf} and C_{max} appear to increase proportionally with dose from 1 mg to 100 mg, with a suggestion of more than proportional increase from 100 mg to 200 mg. Mean terminal t½ was 3.8 to 7.5 hours.

C_{max} and AUC_{inf} of the 100 mg PF-06700841 tablets compared with 100 mg oral suspension were within the 80% to 125% equivalence interval indicating similar bioavailability of the tablet and oral solution/suspension. A high fat meal decreased AUC_{inf} and C_{max} of the 100 mg tablet by approximately 18% and 36%, respectively and delayed T_{max} with a median value of 4.0 hours, compared to a median T_{max} 0.5 hours under fasted conditions. PF-006700841 can be administered with or without food.

On Day 10 of multiple-dose administration in healthy participants, median T_{max} was at or before 1.5 hours postdose across the entire range of doses from a total daily dose of 10 mg up to 175 mg. Plasma C_{max} and AUC_{τ} both appeared to increase proportionally with dose from 10 mg QD to 100 mg QD with a trend towards more than proportional increase from 100 mg to 175 mg QD. Mean terminal t½ ranged from 4.9 to 10.7 hours. Steady state generally appeared to have been reached by Day 8 of once daily (QD) or twice daily (BID) dosing. Urinary recovery of PF-06700841 was low, with less than 16% of the dose recovered unchanged.

On Day 28 of multiple-dose administration in psoriasis participants, median T_{max} was 1 hour to 2 hours. In general, dose-normalized exposure was higher in the 100 mg QD group than in the 30 mg QD group. 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 included a reported t½ value of 87.5 hours for one participant with an anomalous data point at 216 hours postdose. All other participants 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 which is in the range observed for healthy participants.

2.2.3.2. Study B7931009

Following a single oral 100 mg dose of PF-06700841 under fasted conditions in Japanese participants, absorption was rapid with a median T_{max} of 1 hour and a range of 0.5 to 2 hours on Day 1. Following multiple oral dosing on Day 10, median T_{max} was 0.76 hours with a range of 0.5 to 4.0 hours. Steady-state generally appears to have been achieved by Day 6. The mean terminal t½ was 8.9 hours following last dose of 100 mg on Day 10. Urinary recovery of PF-06700841 was similar to Western participants, with less than 16% of the dose recovered unchanged.

PF-06700841 exposures at steady state in Japanese participants appeared to be higher than the exposures in Western participants observed in Study B7931001 (n=6 in each group of Japanese or Western participants).

2.2.3.3. Study B7931004

Overall the PF-06700841 PK behaved consistently across different dose regimens in that the higher concentrations were achieved with higher daily doses in either induction or maintenance periods. Plasma concentrations of PF-06700841 observed over the treatment period indicated that the expected drug exposure was achieved in participants with moderate to severe psoriasis. There was no substantial difference in PF-06700841 concentration-time profiles in psoriasis participants compared to those in healthy participants..

2.3. Benefit/Risk Assessment

There is no clinical experience to date for the topical treatment of patients with psoriasis with PF-06700841. The current study is the first study of PF-06700841 administered topically for the treatment of patients with mild to moderate plaque psoriasis. Based on the clinical data from study B7931004 in patients with moderate to severe psoriasis treated with PF-06700841 orally for 12 weeks, it is anticipated that topical PF-06700841 will have acceptable benefit/risk balance in patients with mild to moderate psoriasis.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of PF-06700841 may be found in the Investigator's Brochure, which is the single reference safety document (SRSD) for this study.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To compare the efficacy of multiple dose levels of PF-06700841 versus vehicle on change from baseline in PASI score in participants with mild to moderate plaque psoriasis.	• Change from baseline in PASI score at Week 12.	• Estimand E1: This estimand is intended to provide a population level estimate of the treatment effect of the IP alone on a continuous endpoint; without the benefit of additional prohibited medications, regardless of participants compliance with the IP dosing. • Population: Participants with mild to moderate plaque psoriasis as defined by the inclusion and exclusion without the benefit of additional prohibited medications regardless of compliance. • Intercurrent Events: A) Prohibited medication – all scores after participants receive prohibited medication will be omitted from the analysis and treated as missing scores. Missing scores will be imputed based on the assumption that participants do not benefit from the IP treatment. B) Withdrawal and all other events leading to missing data will be treated similarly as in A). C) Inadequate compliance – participants data will be used as recorded. • Population level summary: The mean difference between treated and vehicle control arms of the change from baseline PASI score.
Secondary:	**Secondary:**	**Secondary:**
• To compare the efficacy of multiple dose levels of PF-06700841 versus vehicle on PGA score in participants with mild to moderate plaque psoriasis.	Key secondary endpoint • Proportion of participants with PGA score clear (0) or almost clear (1) and ≥2 points improvement from baseline at Week 12.	• Estimand E2: This estimand is intended to provide a population level estimate of the treatment effect of the IP alone on a binary responder endpoint; without the benefit of additional prohibited medications, regardless of participants compliance with the IP dosing. • Population: Participants with mild to moderate plaque psoriasis as defined by the inclusion and exclusion criteria without the benefit of additional prohibited medication regardless of compliance. • Intercurrent Events: A) Prohibited medication –response will be considered negative for participants after receiving prohibited medication.
• To compare the efficacy of multiple dose levels of PF-06700841versus vehicle on the proportion of participants with mild to moderate plaque psoriasis achieving PASI 75.	Proportion of participants achieving PASI 75 (75% or greater improvement from Baseline) at time points specified in the Schedule of Activities (SoA).	

Objectives	Endpoints	Estimands
		B) Withdrawal and all other events leading to missing data will be treated as in A). C) Inadequate compliance – participants data will be used as recorded. • Population level summary: The difference in proportions between treated and vehicle response rates.
• To compare the efficacy of multiple dose levels of PF-06700841 versus vehicle on measures of disease and symptom severity in participants with mild to moderate plaque psoriasis.	• Change from baseline and percent change from baseline in PASI scores at time points specified in the SoA. • Absolute score and change from baseline in Peak-Pruritus Numerical Rating Scale score at time points specified in the SoA. • Absolute score and change from baseline Psoriasis Symptom Inventory at time points specified in the SoA. • Proportion of participants with PGA score clear (0) or almost clear (1) and ≥2 points improvement from baseline at time points specified in the SoA. • The proportion of participants who achieved a Psoriasis Symptom Inventory score of 0 (not at all) or 1 (mild) on every item at time points specified in the SoA.	• All other continuous secondary endpoints will be analyzed descriptively and using estimand E1 described above when appropriate. • All other categorical secondary endpoints will be analyzed descriptively and using estimand E2 described above when appropriate.
• To assess safety and tolerability of PF-06700841 in participants with mild to moderate plaque psoriasis.	• Incidence and severity of adverse events, serious adverse events and withdrawals due to adverse events. • Change from baseline in clinical laboratory values (chemistry and hematology, lipids). • Change from baseline in ECG parameters (heart rate, QT, QTc, PR and QRS intervals). • Change from baseline in vital signs (blood pressure, pulse rate and temperature measurements). • Incidence of severity grades in skin tolerability at times indicated in SoA.	• There is no defined estimand for these endpoints and they will be analyzed using Pfizer data standards as applicable.

Objectives	Endpoints	Estimands
CCI [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted] [redacted]	[redacted]
[redacted]	[redacted] [redacted] [redacted] [redacted] [redacted] [redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Objectives	Endpoints	Estimands
CCI		

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2b, randomized, double-blind, vehicle-controlled, parallel group, multicenter study in participants with mild to moderate plaque psoriasis. The duration of study participation will be approximately 22 weeks, including up to a 6 week screening period, 12 week treatment period, and approximately 4 week follow-up period in both Stage 1 and Stage participants.

The study will be conducted in 2 stages where an additional cohort (Stage 2) of participants may be added, following completion of enrollment into Stage 1 and at the discretion of the Sponsor. Investigators, study participants, and Pfizer study team members will remain blinded to results of Stage 1.

In Stage 1, approximately 240 participants are planned to be randomized into the study, to allow for approximately 192 (20% drop out rate) evaluable participants (approximately 24 completers per arm, 8 arms). Participants will be randomized to 1 of 8 treatment groups in the ratio of 1:1:1:1:1:1:1:1. Participants will be randomized to 1 of 8 treatment groups in QD (4 active and 1 vehicle) or BID (2 active and 1 vehicle) dosing regimen in the ratio of 1:1:1:1:1:1:1:1.

Stage 2 will be undertaken at the discretion of the Sponsor, in order to provide more extensive exploration of the dose response curve. In Stage 2, approximately 40 participants are planned to be randomized to allow for approximately 32 evaluable participants. Participants will be randomized into 1 of 2 treatment groups in BID (1 active and 1 vehicle) dosing regimen, in ratio 3:1.

The eligibility criteria for participants enrolled in Stage 1 and Stage 2 are the same.

A study schematic is shown in Figure 1, treatment groups are shown in Table 2.

Figure 1. Study Schematic

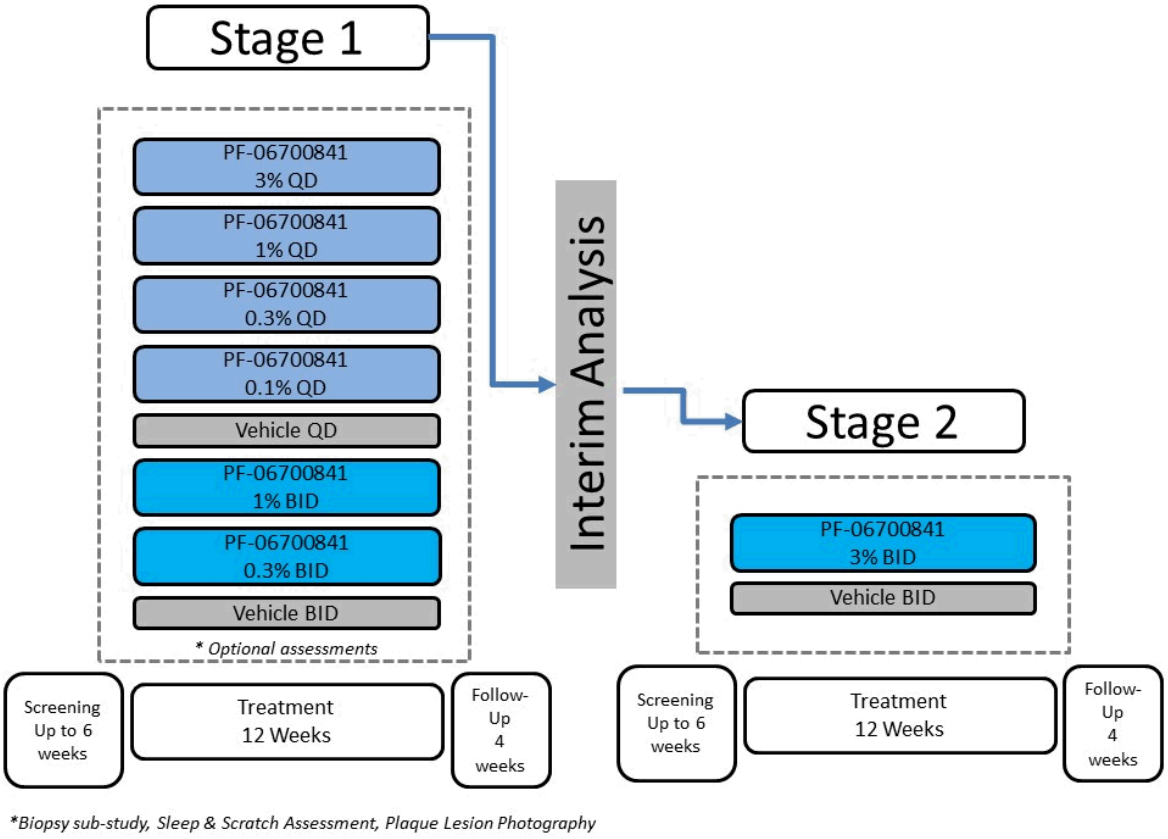

Table 2. Treatment Groups

Stage	Treatment Group	Target Number of Participants Randomized	Approx. Number of Completers	Investigational Product
1	A	30	24	Vehicle cream QD
	B	30	24	PF-06700841 0.1% cream QD
	C	30	24	PF-06700841 0.3% cream QD
	D	30	24	PF-06700841 1.0% cream QD
	E	30	24	PF-06700841 3.0% cream QD
	F	30	24	Vehicle cream BID
	G	30	24	PF-06700841 0.3% cream BID
	H	30	24	PF-06700841 1.0% cream BID
2	I	30	24	PF-06700841 3.0% cream BID
	J	10	8	Vehicle cream BID

CCI [redacted]

CCI [redacted]

Throughout the 12-week treatment period, participants will treat all psoriatic areas identified on Day 1, regardless of clearing or improvement. Any new psoriatic areas occurring after Day 1 will also be treated with IP, provided they are treatment eligible (See Section 6.1.1.1).

Investigators, participants, and the sponsor study team (with the exception of the sponsor supply chain lead) will be blinded as to investigational drug (PF-06700841 cream vs placebo cream [vehicle]) assignment during the conduct of the trial.

An interim analysis will be conducted at the end of Stage 1. Some Pfizer team members and other key stakeholders will become unblinded to the results of Stage 1. Unblinded Pfizer team members will be replaced by blinded team members. Investigators and study participants will remain blinded to the results of Stage 1.

If a participant is withdrawn from IP treatment, the participant will proceed with the Early Termination (ET) and Follow up visits per Schedule of Activities. If a participant uses prohibited medication, guidance in Section 10.9 should be followed.

4.2. Scientific Rationale for Study Design

This study is being conducted to provide data on efficacy, safety, tolerability and pharmacokinetics of PF-06700841 topical cream in the treatment of mild to moderate plaque psoriasis. Oral formulation of PF-06700841 has been studied in several studies, this is the first clinical study for its topical formulation in patients with mild to moderate plaque psoriasis. The study is intended to enable selection of a dose and dosing regimen (QD vs BID) for the future clinical development of topical PF-06700841. The length of the study is based on the nonclinical toxicology package, which supports the planned treatment duration of up to 13 weeks.

Since this is one of the first topical application studies of PF-06700841, CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

Patient reported outcomes will evaluate changes in psoriasis symptoms and health related quality of life. The Psoriasis Symptom Inventory (PSI) and the Peak Pruritus Numeric Rating Scale (PP-NRS) are assessments of the symptoms associated with psoriasis, predominantly itching, redness, scaling, burning, stinging, cracking, flaking and pain. CCI [redacted]

CCI [redacted]

CCI [redacted]

Stage 2 of the study is planned to assess the highest PF-06700841 formulation strength of 3% in BID regimens to allow more extensive exploration of the dose response for PF-06700841 topical cream. The corresponding vehicle arm is also planned with participants being randomized in 3:1 ratio in active versus vehicle arms as enrollment in Stage 2 of the study will commence after completion of Stage 1 enrollment.

4.3. Justification for Dose

The nonclinical safety profile of PF-06700841 following systemic administration to rats and monkeys and following topical application to minipigs supports topical human clinical studies (Section 2.2.1). Dose strengths selected for this study are 0.1%, 0.3%, 1%, and 3% PF-06700841. The highest strength cream was selected based on the maximum solubility of the PF-06700841 in the vehicle. The 0.1% was the lowest concentration tested in in vitro systems and it showed pharmacological activity in human skin in CXCL10 and MMP12, borderline activity in filaggrin and no activity in CCL26, suggesting that it is the concentration at which we begin to observe loss of activity. The clinical translation of these in vitro systems is unknown.

Human systemic exposure following topical application of the PF-06700841 cream formulation was estimated by integrating information from the oral and IV studies in the minipig to provide an estimate of bioavailability and clearance from healthy participants (Study B7931001) following oral administration of 30 mg of PF-06700841, assuming an oral bioavailability (F) of 0.8. The bioavailability following topical application to humans was assumed to be the same as that observed in the minipig (F=0.053). The target dose application is defined as 2 mg formulation/cm^2. With the low project topical bioavailability, it is anticipated that there will be limited contribution to efficacy from systemic drug concentrations. However, the projected systemic concentrations (C_{av}) will be benchmarked against those achieved following oral QD dosing of 30 mg PF-06700841 which has shown clinically relevant efficacy in psoriasis (Section 2.2.2.1). CCI [redacted]

CCI [redacted] he exposure from application of this formulation strength BID is not expected to be associated with a change in the risk:benefit.

IFNα regulates genes involved in antiviral and antiproliferative activities. The 3% cream formulation applied BID or QD is projected to modulate the cytokine at the level of 3.3 and 1.65 x IFNα in vitro IC50. The long-term consequences of this level of inhibition are unknown. The C_{av} of the lower BID and QD formulation strengths were generally at or below the in vitro IC50 value(Table 3).

IL-12 and IL-23 have been implicated in the pathophysiology of chronic plaque psoriasis. The projected systemic C_{av} concentrations following either BID or QD topical application are lower (Table 3) than the in vitro IC50 values for both cytokines except for the 3% formulation applied BID which is predicted to modulate the IL-12 cytokine level at 1.5 x the in vitro IC_{50}. CCI [redacted]

Table 3. Exposure Projection Following Topical Application of a PF-06700841 Cream Formulation, Predicted Margins Relative to 30 mg Oral Once Daily and Multiples of Key Cytokines

Cream Formulation Strength (%)	CCI [redacted]	Absorbed Dose mg/kg	Predicted C_{av}, free (nM)	Predicted Margins Relative to Oral 30 mg QD C_{av}, free	Multiple of IFNα In vitro IC50	Multiple of IL-12 In vitro IC50	Multiple of IL-23 In vitro IC50
3 BID	C	0.28	99.0	1.25	3.3	1.5	0.82
3 QD	C	0.14	49.5	2.5	1.65	0.76	0.41
1 BID	C	0.090	33.0	3.7	1.1	0.50	0.28
1 QD	C	0.045	16.5	7.4	0.55	0.25	0.14
0.3 BID	C	0.028	9.90	12.5	0.33	0.15	0.082
0.3 QD	C	0.014	4.95	25	0.165	0.076	0.041
0.1 QD	C	0.0045	1.65	74	0.055	0.025	0.014

BID = twice daily; CCI [redacted]; IFNα = interferon alpha, IC50 free = 30 nM (human whole blood (lymphocytes); IL-12, IC50 free = 65 nM (human whole blood (lymphocytes); IL-23, IC50 free = 120 nM (human whole blood (lymphocytes) C_{av}, free (30 mg QD healthy participants) =122 nM; fu human=0.61; molecular weight =389; 1 ng/mL = 2.568 nM; QD = daily.

CCI [redacted] This is based on data from the oral toxicology program, using the C_{av} of 1145 nM which was achieved at the NOAEL in the 9 month monkey toxicology study.

The NOAEL in the pivotal topical PF-06700841 13-week study in minipigs was 1.28 mg PF-06700841/cm^2/day, resulting in an ~10-fold dose margin based on an anticipated application rate of 2 mg product/cm^2 and the nonclinical dose of 20 mg product/cm^2.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit.

The end of the study is defined as the date of the last visit of the last participant in the study for the last participant in the trial globally.

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Age and Sex:

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

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

Type of Participant and Disease Characteristics:

2. Participants with a diagnosis of plaque psoriasis (psoriasis vulgaris) for at least 6 months prior to Day 1.

3. Participants with a Physician Global Assessment (PGA) score of mild (2) or moderate (3) at Screening and Day 1.

4. At Screening and Day 1, have plaque psoriasis covering 2%-15% (inclusive) of total body surface area (BSA) on the trunk and/or limbs. Only areas to be treated with the IP will be included in this calculation (See Section 6.1.1.1).

5. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations (Section 5.3), and other study procedures.

Weight:

6. Body Mass Index (BMI) 17.5-35 kg/m^2 (inclusive) and body weight ≥40 kg.

Informed Consent:

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

5.2. Exclusion Criteria

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

Medical Conditions:

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

2. Evidence of other skin conditions (eg, eczema) at the time of screening or Day 1 visit that would interfere with the evaluation of psoriasis.

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

4. Any psychiatric condition, including recent or active suicidal ideation or behavior that meets any of the following criteria at Screening or Day 1:

   - 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) (Section 10.10);

   - 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;

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

5. Current or history of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiovascular, or neurological disease.

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

7. History of infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator within 3 months prior to Day 1. History of infection requiring oral antimicrobial therapy within 2 weeks prior to Day 1.

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

   a. A positive Interferon Gamma Release Assay (IGRA) test or positive Mantoux/Purified Protein Derivative (PPD) tuberculin skin test See Section 8.2.1.1 for details;

   b. Participants with chest radiograph with changes suggestive of or evidence of untreated latent or active TB infection will be excluded. See Section 8.2.1.1 for details;

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

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

10. 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. These excluded malignancies include but are not limited to having 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.

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

12. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or IP application or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

Prior/Concomitant Therapy:

13. Require treatment with prohibited medications(s) and/or procedures (Section 10.9).

14. Require concomitant medications other than those allowed (See Section 6.5), or require new concomitant medications or change in dosage within 7 days or 5 half-lives (whichever is longer) prior to Day 1 or any time between Day 1 and last visit unless allowed in Section 6.5.

Prior/Concurrent Clinical Study Experience:

15. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives prior to Day 1 (whichever is longer).

    - Exception: Investigational biologics should be discussed with the Sponsor Medical Monitor to confirm period of discontinuation required.

    - Exception: Previous administration with any investigational oral or topical TYK2 or JAK inhibitors within 3 months or 5 half- lives prior to Day 1 (whichever is longer).

Diagnostic Assessments:

16. Infected with human immunodeficiency virus (HIV), hepatitis B or hepatitis C viruses.

    - Participants who are hepatitis C (HCV) antibody (Ab) positive require further testing with HCV ribonucleic acid (RNA) Polymerase chain reaction (PCR) and are allowed to enroll if HCV RNA PCR negative.

    - Participants who are HBsAg positive are not eligible for the study.

    - Participants who are HBsAg negative and HBcAb positive should 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 participant is not eligible for the study.

      For Japan only, see Country-Specific Requirements on hepatitis B exclusion criteria (Section 10.8).

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

    - Hemoglobin <11.0 g/dL or hematocrit <30% (<0.30 v/v);

    - White blood cell count <3.0 x 10^9/L (<3000 mm^3);

    - Absolute lymphocyte count of <1.0 x 10^9/L (<1,000/mm^3);

    - Absolute neutrophil count of <1.5 x 10^9/L (<1500/mm^3);

    - Platelet count <100 x 10^9/L (<100,000/mm^3);

- estimates of glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 using serum creatinine or cystatin C based calculation (Section 10.18);

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values greater than 2 times the upper limit of normal (ULN);

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

- Creatinine kinase (CK) >3 times ULN;

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

18. Screening 12-lead electrocardiogram (ECG) that demonstrates clinically significant abnormalities requiring treatment (eg, acute myocardial infarction, serious tachy- or brady-arrhythmias) or that are indicative of serious underlying heart disease (eg, cardiomyopathy, major congenital heart disease, low voltage in all leads, Wolff-Parkinson-White syndrome) and other clinically relevant abnormalities which may affect participant safety or interpretation of study results. If QTcF exceeds 450 ms, the ECG should be repeated two more times and the average of the three QTcF should be used to determine the participant eligibility. Participants with average screening value QTcF >450 milliseconds (ms) should be excluded.

19. A history of additional risk factors for torsade de pointes (TdP) (eg, heart failure [New York Heart Association status of class III or IV], hypokalemia, family history of Long QT Syndrome).

Other Exclusions:

20. 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 Pfizer employees, including their family members, directly involved in the conduct of the study.

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

22. Donation of blood in excess of 500 mL within 8 weeks prior to Day 1.

23. In the opinion of the investigator or Sponsor, the participant is inappropriate for entry into this study.

5.3. Lifestyle Considerations

5.3.1. Contraception

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

5.3.2. 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 Day 1.

Participants should not consume grapefruit or grapefruit juice or citrus fruits eg, Seville oranges, omelos within 7 days prior to Day 1 and until collection of the final pharmacokinetic blood sample.

5.3.3. Vaccination

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

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

5.3.4. Other Lifestyle Requirements

- Participants should not apply occlusive dressing(s) to the areas treated with IP.
- Participants should not swim, bathe, be bathed or have treatment areas washed for at least 4 hours after application of the IP.
- Use of sunscreen and regular moisturizes is permitted, but only on areas which are not treated with IP.
- Participants should avoid prolonged exposure to the sun and not use tanning booths, sun lamps or other ultraviolet light sources during the study. Please see Section 10.9 for details on prohibited light therapy.
- The participant should avoid wiping the IP off the skin and the IP should not be re-applied to areas that were inadvertently wiped until the next scheduled dose.
- When applying the IP, the participant will not be required to wear gloves. However, participants should be instructed to wash their hands with mild soap and water before and after each application.
- If study participants need someone else to assist with applying the IP on hard to reach areas (eg, back), this person must wear gloves to avoid exposure to the IP.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to investigational product/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once if they fail screening due to transitory conditions. Re-screening due to failing inclusion/exclusion criteria with respect to PGA [redacted] is not permitted. Rescreened participants should be assigned a new participant number.

All screening assessments must be repeated during re-screening, with the exception of chest radiograph, HIV, Hepatitis and TB testing. These assessments do not have to be repeated if re-screening is done within 12 weeks of the initial screening visit and these assessments were performed during the initial screening visit.

6. STUDY INTERVENTION

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

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

6.1. Study Intervention(s) Administered

For this study, investigational products are the following:

- PF-06700841 cream, in 0.1%, 0.3%, 1%, and 3% (w/w) strengths; may also be referred to as 1 mg/g, 3 mg/g, 10 mg/g, and 30 mg/g, respectively.

- Vehicle cream; contains all excipients as the PF-06700841 cream except for PF-0670084; may also be referred to as vehicle and/or placebo.

Creams are formulated to contain PF-06700841 in designated strength, light mineral oil, white petrolatum, oleyl alcohol, emulsifying wax, diethylene glycol monoethyl ether, polyethylene glycol 400, 2-phenoxyethanol, and purified water.

Vehicle (no active drug in the formulation) contains light mineral oil, white petrolatum, oleyl alcohol, emulsifying wax, diethylene glycol monoethyl ether, polyethylene glycol 400, 2-phenoxyethanol, and purified water.

All active and vehicle creams will be packaged in laminate tubes containing approximately 54 or 57 grams of either vehicle cream or PF-06700841 cream for topical application. All tubes will be provided in cartons and both will be labeled in a blinded fashion according to local regulatory requirements.

6.1.1. Administration

6.1.1.1. Treated Psoriatic Skin Areas

Psoriasis treatment areas will be those affected by psoriasis on the trunk and/or limbs and will not include scalp, face, neck, palms or soles, nails or intertriginous areas.

Before the initial IP application is performed on Day 1, the psoriasis treatment areas will be identified during the Day 1 Visit and documented in the participant's source document study records. The participant will be provided with documentation of the designated treatment areas.

Treated Psoriatic Areas identified on Day 1 should continue to be treated for the entire duration of the treatment period (12 weeks) even if substantial improvement or clearing of psoriasis occurs.

If new psoriatic areas eligible for treatment (as defined in this section above) emerge during the study, IP should be applied to these new areas after consultation with the Investigator. This may result in an additional unscheduled visit and dispensing of IP. These new areas should also be captured in the participant's source document study records including the date of occurrence. Site staff will review the treatment area list with study participant and update as per Schedule of Activities.

If a participant misses applying a dose, the participant should apply this dose provided this dose should have been applied within the last 6 hours. For longer intervals, the dose should be skipped. The missed dose should be recorded in the dosing diary. The next dose should be applied according to the regular dosing regimen.

6.1.1.2. General Instructions

IP should be applied once a day (around the same time of the day) or twice daily (approximately every twelve hours) based on the assigned treatment arm to all eligible psoriasis treatment areas (See Section 6.1.1.1) starting at Day 1 through Week 12 visit. Last dose for both BID and QD dosing will be applied either prior to or during the Week 12 clinic visit in the morning.

Investigational site staff will demonstrate to the participant the application of IP during Day 1 visit. Site staff will also provide instructions for application of IP at home. During all subsequent in-clinic visits through Week 10 (and potentially Week 12), site staff will observe the application of study IP by study participants and re-train participants if/as needed. The IP will be applied per the instructions in the IP manual.

Site staff will also train the participant on completion of the Dosing Diary starting with the first dose applied in the clinic on Day 1 and continuing through the Week 12 visit. This will be filled in by the participant each time the IP is applied.

Those participants having difficulty reaching treatment-eligible areas (eg, back) may be assisted by another person who will need to apply the IP to the participant according to the IP application instructions. The person assisting with the application must wear gloves to avoid any exposure to the IP.

Participants will be instructed not to wipe the IP off the skin, avoid applying an occlusive dressing to the treated areas, and refrain from swimming or bathing/washing the treated areas within **4** hours after application.

Throughout the study period, topical products described in Section 10.9 are not allowed on areas being treated with the IP.

The investigational drug application regimen should not be modified. Temporary discontinuation and/or permanent discontinuation of the investigational product may be appropriate under some circumstances (See Section 7.1.1).

6.2. Preparation/Handling/Storage/Accountability

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

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

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All study interventions will be accounted for using an investigational product accountability form/record.

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

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

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

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

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

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

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

6.2.1. Preparation and Dispensing

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

The IP will be dispensed in a blinded fashion using an interactive response technology (IRT) system at each in-clinic visit from Day 1 Visit to Week 10 Visit. A qualified staff member will dispense the IP via unique container numbers on the cartons provided, in quantities appropriate for the study visit schedule [redacted]

For doses to be administered at home, the participant should be instructed to maintain the product in its original package provided throughout the course of dosing and return the product and its original package (including empty, partially used and unused tubes) to the site at the next study visit. All previously dispensed IP tubes will be retained by the site. For each participant, IP tubes with caps will be weighed individually or collectively by the study site before dispensing and after return and the weights will be recorded. The sponsor will use the recorded weights to estimate usage (eg, mg/cm^2/application) for each participant. Note that the weight recorded on the IP label is a nominal weight of the IP itself without the weight of the tube.

IP will be assigned to participants during Day 1 Visit once the participant is successfully randomized through the IRT system. The investigator or appropriate delegate at the site will access the IRT system at the Day 1 visit and all subsequent scheduled visits (until Week 10) to receive the correct tube numbers to be dispensed to the participant. All tubes of the IP dispensed or returned will be recorded and documented.

The tool to standardize the IP need calculation across participants and study sites may be provided by the sponsor.

6.2.2. Investigational Product Accountability

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

The participant will be asked to bring all dispensed IP (including empty, partially used and unused tubes) and the dosing diary to the clinic at every visit. Detailed drug accountability records, including tube weights measured in the clinic, will be maintained by study staff for each participant.

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

6.2.3. Destruction of Investigational Product Supplies

The investigator will keep all the IP returned by the participants until destruction is authorized.

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

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

6.3. Measures to Minimize Bias: Randomization and Blinding

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

6.3.1. Allocation to Investigational Product

For this study, the IP is PF-06700841 (or its matching vehicle) topical cream. Participants will be randomized into one of the doses in QD dosing arm or BID dosing arm of PF-06700841 or its matching vehicle.

At the Day 1 visit, provided all inclusion/exclusion criteria have been met, the participant will be randomized to trial medication. The investigative site will contact an interactive response technology (IRT) system (interactive Web-based response [IWR]). Allocation of participants to treatment groups will proceed through IRT. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the

participant number. The site personnel will then be provided with a treatment assignment, randomization number, and dispensable unit (DU) or container number when the IP is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

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

Returned IP must not be redispensed to the participants.

6.3.2. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Sponsor Clinician or Sponsor Medical Monitor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. However, discussion with the Sponsor in advance of unblinding is not required. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF).

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

Participants whose code is broken will be discontinued from treatment, complete early termination visit and follow-up period per Schedule of Activities. Any cases of unblinding will be documented in the study report.

6.4. Study Intervention Compliance

The participant will apply the IP at home and during scheduled in clinic visits as per SoA. Participants will be instructed to complete the Dosing Diary each time IP is applied, starting with the first dose applied in the clinic on Day 1, then through Week 12. Participants will be instructed to bring the Dosing Diary and all dispensed IP supplies in its original package (used as well as unused) to the clinic for weighing at all visits. Participant compliance with IP application will be assessed by site staff at each visit by reviewing e-diary (ie, application of IP each day between in clinic visits). In addition, tube weights will be used to assess compliance by the study team at the end of the study.

Participants with missed doses of IP or additional doses of IP beyond dosing regimen will be re-trained by the site. This re-training will occur at a minimum if participant meets the definition of noncompliance (less than 80% or more than 120% of IP applications as directed by the dosing instructions) but may re-training may be performed by the site even if participants missed a few doses or apply a few additional doses. The sponsor will have the

discretion to withdraw any participant from the study due to non-compliance with the topical application of IP. Investigators should indicate on the appropriate CRF page noncompliance with study intervention and provide an explanation. Inventory control of all IPs must be rigorously maintained throughout the duration of the study until all medication has been accounted for and/or returned to the sponsor. Any discrepancies noted between drug dispensing records and the drug inventory must be reported to Pfizer.

6.5. Concomitant Therapy

Medications taken during Screening will be documented as prior medications. Medications taken after the first dose of IP has been administered will be documented as concomitant medications. All concomitant medications taken during the study must be recorded in study records with indication, daily dose, and start and stop dates of administration. Participants will be queried about concomitant medication (including topical medications and treatments, over-the-counter and prescription medications and treatments, and vaccinations) at each visit. Any new concomitant medications or dose changes to current concomitant medications should be evaluated for potential new or worsening adverse events.

See Section 10.9 on prohibited medications and procedures.

The following concomitant medications are **allowed unless excluded in Prohibited Medications (Section 10.9):**

- Antihistamines.
- Selective leukotriene receptor antagonists (eg, montelukast sodium, zafirlukast), mast cell stabilizers (eg, cromolyn sodium or nedocromil sodium).
- Acetaminophen/paracetamol and ibuprofen.
- Medications for regulation of thyroid function.
- Corticosteroid inhalers and intranasal sprays (provided participants receiving stable dose for at least 1 week before Day 1 and during the treatment period).
- Ophthalmic corticosteroids (provided participants receiving stable dose for at least 1 week before Day 1 and during the treatment period).
- Medications for chronic stable medical conditions (eg, hypertension) provided these are not expected to affect the study assessments. Change in medication for hypertension is allowed.
- Hormone replacement therapy (HRT) and hormone contraception as described in Appendix 4 (Section 10.4).

- Topical treatments applied to areas not treated with IP unless prohibited in Section 10.9.
- Sunscreen and regular moisturizers applied to areas not treated with IP.
- Any other concomitant medication not specifically prohibited in Section 10.9 may be considered on a case by case basis by the investigator in consultation with the Sponsor Medical Monitor.

6.5.1. Rescue Medicine

There is no rescue therapy to reverse the adverse events (AEs) observed with PF-06700841; standard medical supportive care must be provided to manage the AEs.

6.6. Dose Modification

Not applicable.

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to **permanently discontinue** the IP. Per the study estimands, if IP is permanently discontinued, the participant will proceed to early termination and follow up visits per Schedule of Activities. The site will inform Sponsor Medical Monitor or Sponsor clinician if the below criteria for permanent discontinuation of the IP are triggered.

Any participant meeting discontinuation criteria must enter into the Follow up Period with their first follow up visit occurring 1 week after their last dose whenever possible (instead of two weeks in Schedule of Activities) and continue visits per Investigator's discretion 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 participant takes the IP or as soon as possible thereafter. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. 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.

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

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

ECG Changes

A participant who meets either bulleted criterion below based on the average of triplicate ECG readings (see Section 8.2.2.4) will be withdrawn from the IP application.

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

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

Local Tolerability Assessment

If a participant experiences severity Grade 3 (severe) or 4 (very severe) on the local tolerability assessment (Section 8.2.2.8, Table 9), the IP will be discontinued permanently and participant will proceed to ET visit and Follow-up period as described in Schedule of Activities.

If a participant experiences application site reaction of Grade 2 (moderate) on the local tolerability assessment, investigator may temporarily discontinue application of IP for up to one week after consultation with the Sponsor Medical Monitor. This dosing gap may occur only once for the same participant.

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 will be considered, after consultation with the Sponsor clinician or Sponsor Medical Monitor.

Potential Cases of Decreased eGFR

If an individual participant demonstrates CONCOMITANT serum creatinine-based AND serum Cystatin C-based eGFR decline of ≥30% (See Section 10.18) compared to the participant's baseline eGFR, then the participant 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 the investigator.

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

Follow-up evaluations 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 blood urea nitrogen (BUN), serum creatine kinase (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 Sponsor Medical Monitor for review immediately upon receipt by the PI.

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	$<1000/mm^3$; $<1.0 \times 10^9/L$
Hemoglobin	<10.0 g/dL; <6.2 mmol/L; <100 g/L
Platelet count	$<75,000/mm^3$; $<75.0 \times 10^9/L$
Lymphocytes	$<500/mm^3$; $<0.5 \times 10^9/L$
Chemistry	
AST[b]	>2.5x ULN
ALT	>2.5x ULN
Total bilirubin[a]	>1.5x ULN

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

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 Sponsor Medical Monitor.

Pregnancy

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

- Two negative pregnancy tests are required before receiving IP (one negative serum pregnancy test at screening and one negative urine pregnancy test at Day 1 visit). If urine pregnancy test is positive after IP application, serum pregnancy test will be conducted, IP paused and sponsor clinician and sponsor medical monitor notified immediately.

7.1.1. Temporary Discontinuation

Temporary discontinuations of IP:

- Will occur for woman of childbearing potential (WOCBP) in cases of positive urine pregnancy test which if confirmed by serum pregnancy test will lead to permanent discontinuation (see Pregnancy in Section 7.1).

- May apply in case of application site reaction as described in Local Tolerability Assessment in Section 7.1.

- Additional instances of temporary discontinuation may be appropriate (eg, surgery, infection, etc).

All temporary discontinuations should be discussed with Sponsor Clinician or Sponsor Medical Monitor to determine if participant may continue in the study. If possible, the site will consult with the sponsor prior to temporary discontinuation.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Adverse event;

- Refused further follow-up;

- Lost to follow-up;

- Death;

- Study terminated by sponsor;

- Pregnancy;

- Physician decision;

- Other.

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

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

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

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

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

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

Withdrawal of Consent:

Participants who request to discontinue receipt of study treatment will proceed to ET visit as soon as possible. Whenever possible, these participants should have one visit approx. two weeks after the last dose (Week 14 Follow up visit assessments) and the last visit at least 28 days after the last dose of IP was administered (Week 16 Follow-up visit assessments).

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

7.3. Lost to Follow-up

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

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

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

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

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

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

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

The total blood sampling volume for individual participants in this study is approximately 205 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy Assessments

All efficacy assessments of psoriatic skin will be based only on areas treated with IP, described in Section 6.1.1.1.

Efficacy assessments for the same participant should be performed by the same clinician throughout the study whenever possible.

8.1.1. Psoriasis Area and Severity Index

The Psoriasis Area and Severity Index (PASI) quantifies the severity of a participant's psoriasis based on both lesion severity and the percentage of CCI [redacted] affected.[28]

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. Appropriate morphologic descriptors for each severity score are shown in Table 4.

Table 4. Component Scoring Criteria for the Psoriasis Area and Severity Index (PASI)

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

Percent BSA with Psoriasis: the extent (%) to which each of the four body regions is involved with psoriasis is categorized using a non-linear scaling method to a numerical area score according to the following BSA scoring criteria (Table 5).

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

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

Calculating PASI

Body Region Weighting: each body region is weighted according to its approximate percentage of the whole body (Table 6).

Table 6. Area and Severity Index (PASI) Lesions Body Region Weighting

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

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

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

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

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

Calculation of PASI will be done centrally by Sponsor programmers.

8.1.2. Physician Global Assessment

The Physician Global Assessment (PGA) 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 (Table 7). 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. The 5-point scale for PGA is: 0, “clear”; 1, “almost clear”; 2, “mild”; 3, “moderate”; 4 “severe” (Table 8).

Table 7. Component Scoring Criteria for the Physician's Global Assessment (PGA)

Score	Description
Erythema (E)	
0	No evidence of erythema (post-inflammatory hyperpigmentation and/or hypopigmentation may be present)
1	Light pink
2	Light red
3	Red
4	Dark, deep red
Induration (I)	
0	No evidence of plaque elevation

Score	Description
1	Barely palpable
2	Slight, but definite elevation, indistinct edges
3	Elevated with distinct edges
4	Marked plaque elevation, hard/sharp borders
Scaling (S)	
0	No evidence of scaling
1	Occasional fine scale
2	Fine scale predominates
3	Coarse scale predominates
4	Thick, coarse scale predominates

Table 8. Physician's Global Assessment (PGA) Score

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

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

8.1.3. Body Surface Area

Assessment of body surface area (BSA) involved in psoriasis is performed separately for four areas of the body: head, upper limbs, trunk (including axillae and groin), and lower limbs (including buttocks). The percentage surface area affected by psoriasis is estimated by means of the "handprint method", where the full hand of the participant (ie, the participant's fully extended palm, fingers and thumb together) represents approximately 1% of the total BSA.[29]

Body region value is then summed across all four body regions resulting in a total BSA with psoriasis as described in the following equation:

$$BSA\ (\%) = 0.1Sh + 0.2Su + 0.3St + 0.4Sl$$

(where S = body region surface area with psoriasis; h = head & neck; u = upper limbs; t = trunk; l = lower limbs). Calculation will be done centrally by Sponsor programmers.

BSA calculation will be used to determine the number of tubes with IP to be dispensed. BSA assessment and BSA calculation may be also performed during unscheduled visit if participant develops additional treatment eligible psoriatic areas in between in clinic visits.

8.1.4. Rater Qualifications

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

8.2. Safety Assessments

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

8.2.1. Assessments at Screening Only

8.2.1.1. Tuberculosis Testing

Participants will be screened for infection with Mycobacterium tuberculosis (TB) either using Interferon Gamma Release Assay (IGRA) test or Mantoux/Purified Protein Derivative (PPD) tuberculin skin test. This will be performed at Screening. If either of these TB tests were performed within 12 weeks prior to Day 1 and the documentation is available, this does not have to be performed during Screening.

It is recommended that participants with a history of Bacille Calmette Guérin (BCG) vaccination be tested with the IGRA test since the Mantoux/PPD tuberculin skin test may be positive due to vaccination.

8.2.1.1.1. Interferon Gamma Release Assay Tuberculin Test

The following are acceptable IGRA assays: QuantiFERON®-TB Gold Plus test, 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.

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

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

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

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

8.2.1.1.2. Mantoux/Purified Protein Derivative (PPD) Tuberculin Skin Test

Participants can be TB screened using the Mantoux/PPD Tuberculin Skin Test. Mantoux/PPD testing can also be performed if there are indeterminate QFT-G test results. Participants must have a Mantoux/PPD tuberculin skin test administered and then evaluated by a health care professional 48 to 72 hours later. A positive Mantoux/PPD tuberculin skin test is exclusionary.

8.2.1.2. Chest Radiograph

Local guidelines should be followed with respect to whether chest radiograph should or should not be taken at Screening. For example, in the United States, local guidelines require chest radiograph in high-risk population. In the event a chest radiograph is taken, it should be read by a qualified radiologist. In addition, local guidelines should be followed as to which imaging method should be used. Examples of imaging methods are X-ray (posterior-anterior and lateral views are recommended), computed tomography (CT) or magnetic resonance imaging (MRI). Documentation of the official reading should be located and available in the source documentation.

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

Participants with evidence of currently active TB, general infections, heart failure or malignancy will be excluded. Participants with changes suggestive of untreated latent or active TB infection may be enrolled after consultation with a pulmonary or infectious disease specialist who determines a low risk of infection.

8.2.1.3. Medical History

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

History of alcohol and tobacco use, current smoking status and average alcohol consumption will be collected in units. A unit of alcohol contains 12 g of pure alcohol, an amount equivalent to that contained in 5 oz/150 mL (a glass) of wine, 12 oz/360 mL of beer, or 1.5 oz/45 mL of 90 proof of spirits.

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

8.2.1.4. Suicidal Ideation and Behavior Risk Monitoring

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

8.2.1.4.1. Columbia Suicide Severity Rating Scale

The Columbia Suicide Severity Rating Scale (C-SSRS) is a validated tool to evaluate suicidal ideation and behavior[30] (Section 10.10).

8.2.2. Assessment during Study

8.2.2.1. Full Physical and Brief Physical Examinations

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

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

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

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

8.2.2.2. Weight and Height

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

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

8.2.2.3. Vital Signs

Temperature (Oral, Tympanic, Axillary or Temporal), pulse rate and blood pressure will be assessed. It is preferred that body temperature be collected using the same method for the same participant throughout the study.

Blood pressure and pulse rate measurements will be assessed with a completely automated device either in supine or sitting position. The same position should be used consistently for the same participant throughout the entire study. Manual techniques will be used only if an automated device is not available. It is preferred that the same arm (preferably the dominant arm) be used throughout the study. Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest.

8.2.2.4. Electrocardiograms

Single 12-Lead ECGs should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex. Additional ECG may be performed upon request by the Sponsor Clinician or the Sponsor Medical Monitor. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 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.

ECGs will be read and interpreted locally. To ensure safety of the participants, a qualified individual (eg, investigator, sub-investigator) at the investigator site will make comparisons to baseline measurements taken at Day 1. ECG parameters (heart rate, QT, QTcF, PR and QRS intervals) should be recorded on the Case Report Form (CRF). A copy of the ECG should be available as source documents for review.

During screening, if participants have initial screening value QTcF >450 milliseconds (ms), ECG should be repeated two more times and the average of the three QTcF should be used to determine the participant eligibility.

If at any subsequent time QTcF ≥500 msec or change from baseline QTc ≥60 msec, ECG should be repeated two more times and an average of these values should be used to determine withdrawal from IP (see Section 7.1). If the average is above these thresholds, participants should be monitored hourly with triple ECGs.

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

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

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

8.2.2.5. Clinical Safety Laboratory Assessments

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

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

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

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

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

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

8.2.2.6. Herpetiform Rash

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

8.2.2.7. Creatinine, Cystatin C, and estimates of Glomerular Filtration Rate

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. Serum 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.

Serum creatinine will be measured as part of serum chemistry at times specified in the Schedule of Activities section of the protocol. Creatinine elevations above the ULN will be followed until resolution or baseline. Serum creatinine based eGFR will be calculated. Serum cystatin C will be measured and cystatin C based eGFR will be calculated at corresponding times per Schedule of Activities.

The eGFR will be calculated using the 2 sets of equations developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI),[31] which utilize serum creatinine (SCr) and serum Cystatin C (S Cystatin C) respectively (Section 10.18).

8.2.2.8. Local Tolerability Assessment

The investigator or designee will assess tolerability at the site of IP application. This assessment will focus on the treated non-lesional skin surrounding the plaques using scale[32] in Table 9. See Section 7.1 for permanent and temporary discontinuation criteria based on local tolerability assessment.

Table 9. Skin Tolerability Grading System

Grade	Severity	Description
0	None	No evidence of local intolerance
1	Mild	Minimal erythema and/or oedema, slight glazed appearance
2	Moderate	Definite erythema and/or oedema with peeling and/or cracking but needs no adaptation of posology
3	Severe (to be reported as an AE)	Erythema, oedema glazing with fissures, few vesicles or papules: consider removing topical agent (if still in place)
4	Very severe (to be reported as an AE)	Strong reaction spreading beyond the treated area, bullous reaction, erosions: removal of topical agent (if still in place)

8.2.2.9. Pregnancy Testing

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

8.3. Adverse Events and Serious Adverse Events

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

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

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

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

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

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

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

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

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

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

8.3.1.1. Reporting SAEs to Pfizer Safety

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

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

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

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

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

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

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 28 days after the last dose of IP.

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

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

8.3.5.2. Exposure During Breastfeeding

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

8.3.5.3. Occupational Exposure

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

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

8.3.6. Medication Errors

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

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

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

Medication errors include:

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

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

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

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

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

8.4. Treatment of Overdose

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

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities until investigational product can no longer be detected systemically (at least 7 days).
3. Obtain a blood sample for pharmacokinetic (PK) analysis within 1 day from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

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

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

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

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8.9. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.10. Patient Reported Outcome Measures

Every effort should be made for the participant to complete all patient reported outcome (PRO) questionnaires before any other assessments. All PROs should be completed in the following order: Psoriasis Symptom Inventory (PSI), Peak-Pruritus Numerical Rating Scale (PP-NRS), CCI [redacted] The amount of time required for a participant to complete the PRO questionnaires is approximately 10-30 minutes (depending on the visit and associated PROs).

Once participants meet all inclusion/exclusion criteria, they will be provided a handheld device (provided by the Sponsor) for dosing diary and ePROs completion as per the time points defined in the Schedule of Activities.

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

8.10.1. Psoriasis Symptom Inventory

The Psoriasis Symptom Inventory (PSI) is a self-administered 8 item questionnaire that measures the severity of psoriasis symptoms over the past 24 hours and the past 7 days.[33] For the first 2 weeks up to Week 2 visit (inclusive), the PSI will be administered daily using a recall period of 24 hours. After Week 2 visit, the PSI will be administered according to the Schedule of Activities using a recall period of past 7 days. The measure includes concepts of itch, pain, burning, stinging, cracking, scaling, flaking, and redness. Patients are asked to respond to each item using a 5-point Likert response scale: 0: not all severe, 1: mild, 2: moderate, 3: severe and 4: very severe. PSI should be completed as described in the Schedule of Activities.

8.10.2. Peak-Pruritus Numerical Rating Scale

The intensity of pruritus will be assessed by a Peak-Pruritus Numerical Rating Scale (PP-NRS), an 11-category numeric rating scale from 0 to 10, which is patient reported (Section 10.11).[34,35] Participants will be asked to assess their itch over the past 24 hours, with the terms “no itching” (0) and “worst possible itching” (10).

The PP-NRS should be completed as described in the Schedule of Activities, preferably the same time of the day.

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9. STATISTICAL CONSIDERATIONS

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

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The primary estimand will be the population average treatment effect on change from baseline in PASI scores at Week 12 relative to vehicle (with the same dosing schedule, QD or BID) without regard to compliance in the absence of prohibited medication. Measurements after the initiation of prohibited medication will be censored and treated as missing data. Missing data due to censoring, study withdrawal or other reasons will have data imputed using a control based multiple imputation strategy assuming these participants no longer receive an efficacy benefit from the IP but rather, have a response similar to participants assigned to vehicle. Participants with inadequate compliance will have their recorded PASI scores used as-is in the analysis. The population based treatment effect will be the differences in the mean change from baseline in each treatment arm compared to the corresponding vehicle.

The secondary estimand will be the population average treatment effect on the PGA response rate (percentage of participants with a score of clear (0) or almost clear (1) and ≥2 point improvement from baseline at Week 12 relative to vehicle (with the same dosing schedule, QD or BID) without regard to compliance with IP in the absence of prohibited medication. This is a composite estimand where success is defined as achievement of a PGA response while remaining on study, providing data and not taking prohibited medication; lack of compliance or adverse events will not be counted as a failure. The population based treatment effect will be the differences in the proportions of successes in each treatment arm compared to the corresponding vehicle.

All other key secondary continuous clinical endpoints will be analyzed using the primary estimand, while all other key secondary categorical clinical endpoints will be analyzed using the secondary estimand described above. CCI [redacted] Other estimands may be used for some of the primary and secondary endpoints as a means to examine the robustness of the results and to compare to available literature as needed. Details of these analyses will be presented in the statistical analysis plan (SAP).

9.2. Sample Size Determination

The sample size of Stage 1 and Stage 2 are based on the primary efficacy endpoint, PASI change from baseline at Week 12. With an assumed standard deviation of 4.2 and treatment difference of 4.5, a total of 240 randomized participants with 8 treatment groups from Stage 1 will provide approximately 90% power for individual comparisons of active groups versus vehicle groups at a one-sided significance of 0.05 using a Bonferroni multiplicity adjustment. This calculation allows for an approximate 20% dropout rate, that is 24 participants evaluable per arm at Week 12, where evaluable is defined as included in the mITT set (defined in Section 9.3).

Participants enrolled in Stage 2 will be randomized to either the 3% BID treatment group or the corresponding vehicle BID group in 3:1 randomization ratio. During the final analysis process, participants from BID vehicle group from both Stage 1 and Stage 2 will be pooled together for the comparisons of the BID treatment groups. With an assumed standard deviation of 4.2 and treatment difference of 4.5, a total of 40 participants in Stage 2 will provide approximately 90% power with one-sided significance level using Bonferroni correction on 7 pairwise comparisons.

9.3. Populations for Analysis

For purposes of analysis, the following populations are defined:

Population	Description
Safety Analysis Set	All participants randomly assigned to IP and who apply at least 1 dose of IP. Participants will be analyzed according to the product they actually received. For participants who discontinue treatment and/or receive prohibited medication, efficacy data (eg, primary and key secondary endpoints) will be censored starting at the ET visit.

Defined Population for Analysis	Description
mITT analysis set	All participants randomly assigned to IP and who apply at least 1 dose of IP.
CCI [redacted]	[redacted]

9.4. Statistical Analyses

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

9.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary: Change from Baseline PASI at Week 12	A landmark analysis using analysis of covariance of change from baseline PASI, adjusting for the baseline PASI score, to estimate the effect of the initially randomized treatment in the absence of prohibited medication regardless of treatment compliance. The analysis will use the mITT analysis set. At the interim, BID treatment groups (PF-06700841 1% and 0.3% BID) will be compared against the available BID vehicle group data, whereas all BID treatment groups will be compared against the pooled BID vehicle group from two stages during the final analysis. Missing data due to any cause including censoring due to initiation of prohibited medication will be imputed using the corresponding vehicle arm, missing data in a vehicle arm will be imputed using data from the vehicle arm assuming data are missing at random (MAR). The analysis will combine the results from the multiple imputations using Rubin's rule's as implemented in SAS PROC MIANALYZE. The overall family wise Type I error rate will be controlled at the one-sided 0.05 level using the Hochberg step up procedure.
Secondary – PGA Response at Week 12	A landmark analysis of the composite endpoint; achieving a PGA response (a score of clear(0) or almost clear(1) and ≥2 point improvement from baseline) without prohibited medication, while remaining on study and providing data. The analysis will use the mITT analysis set. Based on the definition of the composite endpoint all participants in the mITT set will have a response for all visits (ie, there is no missing data). The proportions responding and the risk difference between treated arms and their corresponding vehicle control arm will be analyzed using an unconditional exact method: risk differences and corresponding 2-sided unconditional exact 90% confidence intervals will be computed using the Chan and Zhang (1999) method. No adjustments for multiplicity will be made.

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

Other binary secondary endpoints at time points specified in the Schedule of Activities including, CCI [redacted], PASI75, CCI [redacted], PGA of clear or almost clear and proportions of participants achieving a Psoriasis Symptom Inventory Score of 0 or 1 will be analyzed as described for the secondary estimand along with descriptive statistics and possibly graphical displays. No adjustments for multiplicity will be made for these endpoints.

CCI [redacted]

Sensitivity analysis on baseline charactersistics about the primary and key secondary endpoints by stage and treatment may be conducted and the details of those analysis will be presented in the statisticial analysis plan (SAP) and will be finalized before Stage 1 interim analysis.

9.4.2. Safety Analyses

All safety analyses will be performed on the safety population.

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

9.4.2.1. Electrocardiogram Analyses

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

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

Safety QTc Assessment

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

In addition, the number of participants with uncorrected QT values >500 msec will be summarized.

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9.5. Interim Analyses

An interim analysis will be performed by an Internal Review Committee (IRC) which will include safety and efficacy for making internal business decisions regarding future study planning. If the IRC is asked to perform an analysis of the data, then, the decision criteria, dissemination plan and method of maintaining the study blind as per Pfizer's SOPs will be documented and approved in the IRC charter. Members of the IRC will be qualified and experienced in reviewing and interpreting clinical study data. They will be independent of the study team, and unblinded to treatment. In addition, the analysis details must be documented and approved in an interim analysis SAP or final SAP.

In addition, an interim analysis will be conducted at the end of Stage 1. Some Pfizer team members and other key stakeholders will become unblinded to the results of Stage 1. Unblinded Pfizer team members will be replaced by blinded team members. Investigators and study participants will remain blinded to the results of Stage 1.

9.5.1. Data Monitoring Committee

This study will use an internal review committee (IRC). The IRC will be responsible for ongoing monitoring of safety and efficacy of participants in the study according to the charter. Members of the IRC will be qualified and experienced in reviewing and interpreting clinical study data. They will be external to and independent of the study team, and unblinded to treatment. The recommendations made by the IRC to alter the conduct of the study will be forwarded to Pfizer for final decision. This will not include the members of the study team. 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.

In addition, an external blinded adjudication committee will be selected on ad-hoc basis if suspected cardiovascular and/or thromboembolic events (TE) are observed during the study conduct. The adjudication committee members will consist of external experts and the decisions of the adjudication committee may be databased and used for the analyses of the secondary endpoint and other endpoints. Specific details on this process and additional information can be obtained in the central adjudication committee charter. Other safety events for adjudication may be identified and included in the remit of the safety adjudication committee as appropriate.

9.6. CCI PD Unblinding Plan

A CCI PD unblinding plan approved by the clinical lead, clinical pharmacology lead and statistical lead will be in place to describe the procedures to be employed in safeguarding the study blind for members of the study team. These procedures will be in accordance with applicable Pfizer SOPs for releasing randomization codes and breaking the study blind.

Under this plan a group of statisticians, CCI PD data provider, CCI PD analyst and CCI PD support would be unblinded in order to initiate the building of statistical models of the PK, dose/response as well as exposure/response analysis models and conduct associated simulations. The aim of this work would be to facilitate a fuller interpretation of the study upon completion (at appropriate interim milestone). This group will not serve on the study team during the period of early unblinding. The unblinding may occur after approximately 50% of the participants have completed treatment in Stage 1 and Stage 2. The details of the procedures will be described in the CCI PD Unblinding Plan for Modelling and Simulation for Study B7931023 which will be finalized prior to the start of the CCI PD unblinding.

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10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines;
- Applicable laws and regulations, including applicable privacy laws.

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

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

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, 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 participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

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

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

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

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

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

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

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

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

Participants who are rescreened are required to sign a new ICD.

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10.1.4. Data Protection

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

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

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

10.1.5. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

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

EudraCT

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

www.pfizer.com

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

Documents within marketing authorization packages/submissions

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

Data Sharing

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

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

10.1.6. Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

10.1.7. Source Documents

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

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

Definition of what constitutes source data can be found in Study completion guidelines.

10.1.8. Study and Site Closure

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

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

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

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

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

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor's Qualified Medical Personnel

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

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

10.2. Appendix 2: Clinical Laboratory Tests

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

Table 10. Protocol-Required Laboratory Assessments

Hematology[a]	Chemistry[a]	Urinalysis[a]	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Reticulocyte count Platelet count WBC count with differential Total neutrophils (%, Abs) Eosinophils (%, Abs) Monocytes (%, Abs) Basophils (%, Abs) Lymphocytes (%, Abs)	BUN/urea and creatinine Cystatin C Glucose Calcium Sodium Potassium Chloride Total CO2 (bicarbonate) AST, ALT GGT Total, indirect and direct bilirubin Alkaline phosphatase Uric acid Albumin Total protein Creatine kinase (CK)[b]	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[d]	At screening only: • FSH[e] • HIV • Hepatitis B Surface Antigen (HBsAg) • Hepatitis B Core Antibody (HBcAb) • Hepatitis B Surface Antibody (HBsAb)[f] • Hepatitis C antibody (HCV Ab) • Hepatitis C RNA PCR[g] • TB test[h] • aPTT • PT/INR At visits per SoA: • Pregnancy test (β-hCG)[i] • HBV DNA[j] (Japan only) • Skin swabs for herpetiform rash[k] CC [redacted] • Lipid Profile Panel[c] Total Cholesterol Triglycerides HDL LDL

Abbreviations: Abs = absolute; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; CO_2 = carbon dioxide; FSH = follicle-stimulating hormone; GGT = Gamma Glutamyl Transferase; HBcAb = Hepatitis B Core Antibody; HBsAb = Hepatitis B Surface Antibody; HBsAg = Hepatitis B Surface Antigen; HBV DNA = viral load; HC Ab = Hepatitis C Virus Antibody; HCV RNA = Hepatitis C Virus Ribonucleic Acid; HDL = high density lipoproteins; HIV = Human Immunodeficiency Virus; CCI [redacted] IGRA = Interferon Gamma Release Assay; INR = international normalized ratio; LDL =low density lipoproteins; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PCR = polymerase chain reaction; PPD = purified protein derivative; qual = qualitative; PT = prothrombin time; QFT-G = quantiferon-TB-Gold; RBC = red blood cell; WBC = white blood cell

a. Safety labs include hematology, chemistry and urinalysis. Lipid panel will be performed at times indicated in Schedule of Activities. Fasting not required unless lipid panel taken.

   Safety laboratory tests may be performed at a local laboratory, where allowable by law or local guidance, if the study participant is unable to visit the study site. Local laboratory reference ranges and a copy of local lab results should be included in participant's source documents.

b. CK fractionationation if CK > 3x ULN.

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

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

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

f. HBsAb reflex testing only if HBsAg negative but HBcAb positive.

g. HCV RNA reflex testing only if positive for HCV Ab.

h. TB test may be Interferon Gamma Release Assay (IGRA) or Mantoux/Purified Protein Derivative (PPD).

i. For women of childbearing potential.

j. For participants who are HBsAg negative, HBcAb positive, and HBsAb positive OR for participants who are HBsAg negative, HBcAb negative and HBsAb positive without documentation of prior HBV vaccination.

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

Investigators must document their review of each laboratory safety report.

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

10.3.1. Definition of AE

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

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

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations

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

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

AE and SAE Recording/Reporting

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

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

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	**None**	All (and exposure during pregnancy [EDP] supplemental form for EDP)

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

Assessment of Intensity

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

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

rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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

Assessment of Causality

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

accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

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

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

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

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

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

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

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

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

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, as described below during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

  OR

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

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

OR

- Is a WOCBP and is abstinent from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and be the preferred and usual lifestyle of the participant.

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

10.4.3. Woman of Childbearing Potential (WOCBP)

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

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

Women in the following categories are <u>not</u> considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female:

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

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

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

10.4.4. Contraception Methods

Highly Effective Methods That Have Low User Dependency

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

2. Intrauterine device (IUD).

3. Intrauterine hormone-releasing system (IUS).

4. Bilateral tubal occlusion.

5. Vasectomized partner.

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

Highly Effective Methods That Are User Dependent (must be used with another effective method, see below)

1. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - oral;

    - intravaginal;

    - transdermal;

    - injectable.

2. Progestogen-only hormone contraception associated with inhibition of ovulation:

    - oral;

- injectable.

Effective Methods

1. Male or female condom with or without spermicide.

2. Cervical cap, diaphragm, or sponge with spermicide.

3. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

Collection of Pregnancy Information

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

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

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

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

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

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

integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

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

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

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

CCI [redacted]

[redacted]

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments [and Study Intervention Rechallenge Guidelines]

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as Adverse Events (AEs)

- Marked sinus bradycardia (rate <40 bpm) lasting minutes.
- New PR interval prolongation >280 msec.
- New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline.
- New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm.
- New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration.
- Frequent premature ventricular complexes (PVCs), triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.

ECG Findings That <u>May</u> Qualify as Serious Adverse Events (SAEs)

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

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

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

ECG Findings That Qualify as Serious Adverse Events

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

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

10.8. Appendix 8: Country-Specific Requirements

10.8.1. Appendix 8.1: Japan

Exclusion criterion for hepatitis B

In Japan, all participants must undergo testing for HBV surface antigen (HBsAg), HBV core antibody (HBcAb), and HBV surface antibody (HBsAb). This will be performed in CLIA (Clinical Laboratory Improvement Amendments) certified laboratory.

- Participants who are negative for all three serology tests may be eligible.
- Participants who are HBsAg positive will be excluded.
- Participants who are HBsAg negative, HBcAb negative and HBsAb positive and provide a documentation of prior HBV vaccination, may be eligible for the study and will not require HBV DNA monitoring during the study.
- Participants who are HBsAg negative, HBcAb negative and HBsAb positive without documentation of prior HBV vaccination AND participants who are HBsAg negative, HBcAb positive, and HBsAb positive, will have HBV DNA assessed at screening.
    - If detectable HBV DNA, participants will be excluded.
    - If not detectable HBV DNA, participants may be eligible. If enrolled, HBV DNA will be also assessed at Week 12 for these participants.

10.9. Appendix 9: Prohibited Medications & Procedures

The following medications & procedures are prohibited until the last Follow-up visit, unless stated otherwise. If a participant receives prohibited medication or procedure, the investigator should either 1) ask the participant to stop IP immediately and schedule ET visit as soon as possible with follow-up visits per Schedule of Activities or 2)contact Sponsor Clinician or Sponsor Medical monitor to determine if participant may stay in the study. This will be based on the table below. Medications listed below are prohibited even if used for a different indication than noted below.

Drug classes and/or drugs and/or procedures	**Timeframe of restriction prior to Day 1 visit**	**If taken, then**	
		stop IP, proceed to ET and F/UP	**Contact Sponsor**
Anti-coagulants or medications known to cause **thrombocytopenia** **Medications prolonging QT interval**	5 half lives	X	
Light therapy • Narrow-band Ultraviolet B light (UVB); • Broadband phototherapy; • Ultraviolet A light (UVA); • Excimer laser (308 nm).	1 month		X
Any **cell-depleting agents**, including but not limited to • Rituximab; • Alemtuzumab [CamPath®]; • Alkylating agents [eg, cyclophosphamide or chlorambucil]; • Total lymphoid irradiation, etc.	6 months or 5 half-lives, whichever is longer OR until lymphocyte count returns to normal, whichever is longer	X	
Anti-psoriasis biologics • Efalizumab (Raptiva®); • Certolizumab pegol (Cimzia®); • Alefacept (Amevive®); • Infliximab (Remicade®) and biosimilar; • Adalimumab (Humira®) and biosimilar.	2 months	X	
• Ustekinumab (Stelara®); • Secukinumab (Cosentyx); • Ixekizumab (Taltz); • Brodalumab (Siliq®); • Guselkumab (Tremfya®); • Tildrakizumab; • Risankizumab.	3 months	X	
• Etanercept (Enbrel®) and biosimilar	1 month	X	
Systemic treatments other than biologics that could affect psoriasis, including but not limited to: • oral or injectable (eg, intraarticular, intramuscular, or intravenous) corticosteroids;	2 weeks	X	

Drug classes and/or drugs and/or procedures	Timeframe of restriction prior to Day 1 visit	If taken, then	
		stop IP, proceed to ET and F/UP	Contact Sponsor
• retinoids; • methotrexate; • cyclosporine; • fumaric acid derivatives; • sulfasalazine; • hydroxycarbamide (hydroxyurea); • azathioprine; • intramuscular gold; • Otezla (Apremilast®); • Any herbal medicine; • Other systemic treatments known to possibly worsen psoriasis unless on a stable dose for >12 weeks (eg lithium, β-blockers, angiotensin-converting enzyme inhibitors, synthetic anti-malarials, anticonvulsants, antidepressants, cyclosporine, testosterone/estrogens, imiquimod, calcium channel blockers, etc).			
• Psoralens.	1 month		X
• Tofacitinib; • Any other oral JAK inhibitors.	1 month or 5 half –live whichever is longer	X	
Topical treatments applied on psoriasis areas treated with IP and which could affect psoriasis. If applied to other areas not treated with IP, this is allowed. Including but not limited to: • Corticosteroids; • Tars; • Keratolytics; • Anthralin; • vitamin D analogues; • retinoids.	2 weeks	X	
• sunscreens, moisturizers or non-medicated emollients.	2 weeks		X
• Any topical JAK inhibitors.	1 month or 5 half –live whichever is longer	X	

CYP3A4, 5, 7 Inhibitors
• HIV antivirals:
  • delavirdine (Rescriptor®);
  • indinavir (Crixivan®);
  • nelfinavir (Viracept®);
  • ritonavir (Kaletra®, Norvir®);
  • saquinavir (Fortovase®);
• cimetidine (Tagamet®);
• ciprofloxacin (Cipro®);
	1 month or 5 half-lives, whichever is longer	X	

Drug classes and/or drugs and/or procedures	Timeframe of restriction prior to Day 1 visit	If taken, then	
		stop IP, proceed to ET and F/UP	Contact Sponsor
• 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®); • Itraconazole; • Erythromycin; • protease inhibitors; • verapamil; • diltiazem.			
• Amiodarone.	10 months	X	
CYP3A Inducers • 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®).	1 month or 5 half-lives, whichever is longer		X
Strong P-gp inhibitors • Quinidine.	1 month or 5 half-lives, whichever is longer	X	
Substrates of MDR1 • Digoxin.	1 month or 5 half-lives, whichever is longer	X	
Substrates of OCT2/MATE • Dofetilide.	1 month or 5 half-lives, whichever is longer	X	
Vaccination with live or attenuated live vaccine (See Section 5.3.3)	6 weeks	X	

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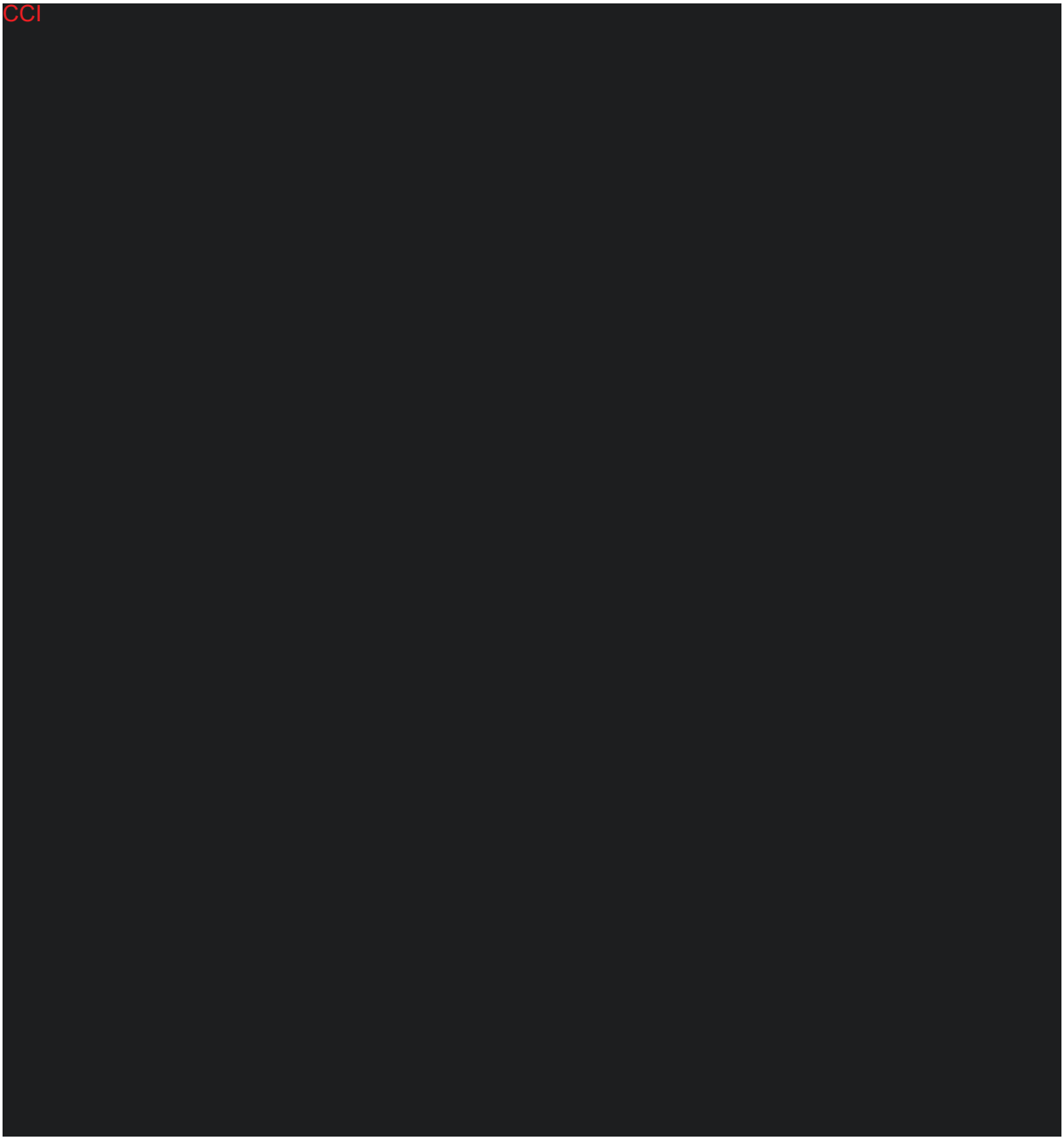

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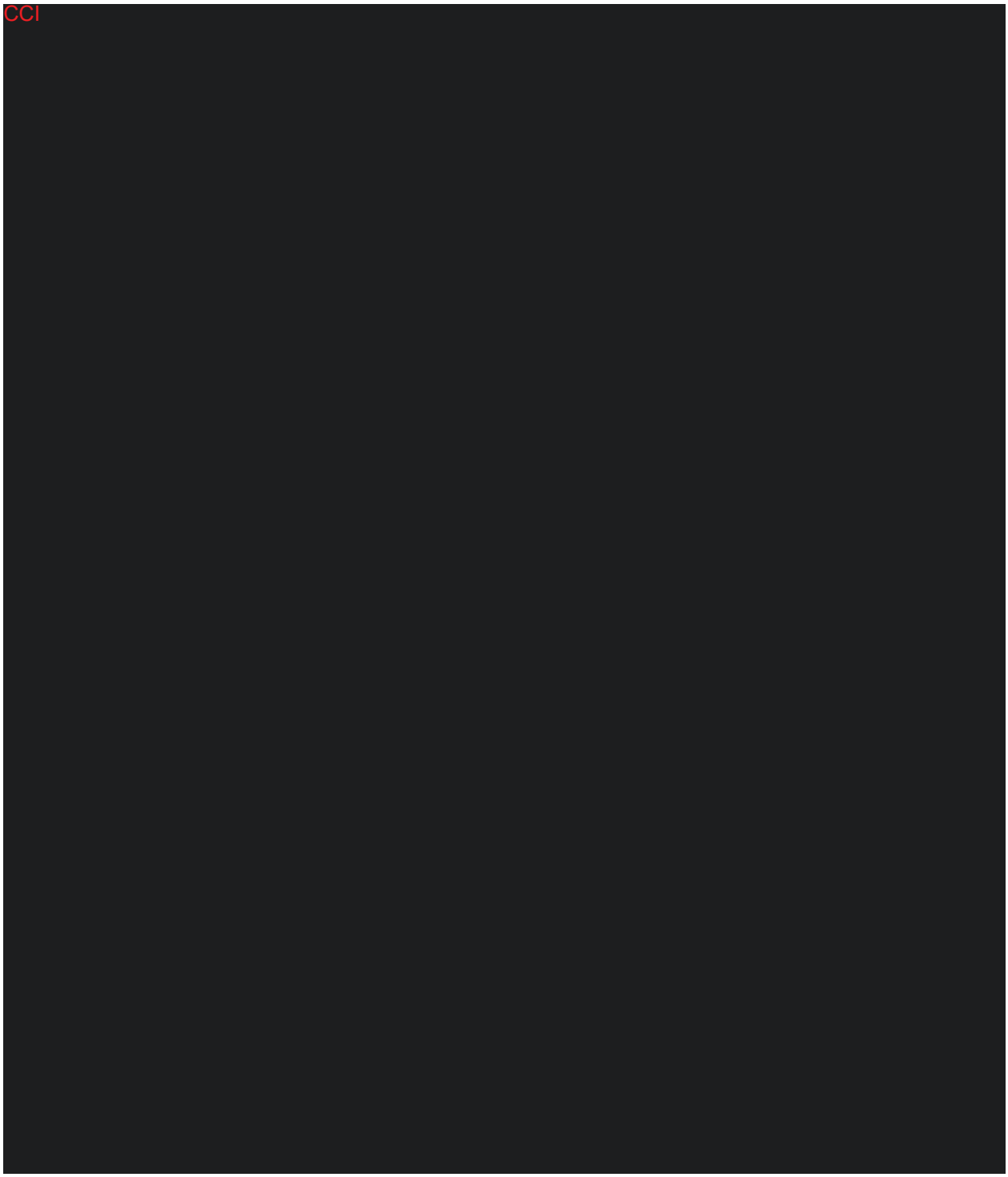

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10.18. Appendix 18: eGFR calculations

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.

CKD-EPI$_{2009Scr}$

If female and SCr is ≤0.7 mg/dL:

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

If female and SCr is >0.7 mg/dL:

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

If male and SCr is ≤0.9 mg/dL:

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

If male and SCr is >0.9 mg/dL:

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

CKD-EPI$_{2012cys}$

If female and Scys is ≤0.8 mg/L:

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

If female and Scys is >0.8 mg/L:

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

If male and Scys is ≤0.8 mg/L:

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

If male and Scys is >0.8 mg/L:

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

10.19. Appendix 19: Abbreviations

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

Abbreviation	Term
AA	Alopecia aereata
Ab	antibody
Abs	absolute
ADA	antidrug antibodies
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{24}	area under the concentration-time curve from time 0 to 24 hours after dose
AUC_{inf}	area under the concentration-time curve from zero to infinity
AUC_{tau}	area under the concentration-time curve during any dosing interval at steady state
AV	atrioventricular
BA	bioavailability
BBS	biospecimen Banking System
BCRP	breast cancer resistance protein
BE	bioequivalence
β-hCG	beta-human chorionic gonadotropin
BID	twice daily
BMI	body Mass Index
BP	blood pressure
bpm	beats per minute
BSA	body surface area
BUN	blood urea nitrogen
C_{av}	Average concentration
CCL26	chemokine ligand 26
CD	Crohn's disease
CDK-EPI	Chronic Kidney Disease Epidemiology Collaboration
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CL	clearance
CLIA	clinical laboratory improvement amendments
C_{max}	maximum observed concentration
CMC	Chemistry, Manufacturing, and Controls
CO	Cross-over
CO_2	carbon dioxide (bicarbonate)

Abbreviation	Term
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSF	cerebrospinal fluid
CSR	clinical study report
C-SSRS	Columbia suicide severity rating scale
CT	clinical trial; computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	clinical trial management system
CV	cardiovascular
CXCL10	C-X-C motif chemokine ligand 10
CYP450	cytochrome P 450
DCT	data collection tool
DDI	drug drug interaction
DILI	drug-induced liver injury
CCI	[redacted]
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DRE	disease-related event
DU	dispensable unit
EBV	epstein barr virus
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EDR	extemporaneous dispensing record
eGFR	estimates of glomerular filtration rate
EMA	European Medicines Agency
EOT	end of treatment
EPO	erythropoietin
ePRO	electronic patient reported outcomes
CCI	[redacted]
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
F	bioavailability
FACS	fluorescent activated cell sorting
FSH	follicle-stimulating hormone
FU	fraction unbound
GCP	Good Clinical Practice

Abbreviation	Term
GGT	gamma-glutamyl transferase
GM-CSF	granulocyte-macrophage colony-stimulating factor
HbA_{1c}	hemoglobin A_{1c}
HBcAb	hepatitis b core antibody
HBsAg	hepatitis b surface antigen
HBV	hepatitis b virus
HCV	hepatitis c
HCV Ab	hepatitis c antibody
HDL	high-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
CCI [redacted]	[redacted]
Hrs	hours
HRT	hormone replacement therapy
HS	hidradenitis suppurativa
CCI [redacted]	[redacted]
IB	investigator's brochure
ICD	informed consent document
ICH	international council for harmonisation
IFN-alpha	interferon alpha
ID	identification
IGRA	interferon gamma release assay
IL-12	Interleukin 12
IMP	investigational medicinal product
IND	investigational new drug application
INR	international normalized ratio
IP	Investigational product
CCI [redacted]	[redacted]
IR	Immediate release
IRAK	interleukin-1 receptor-associated kinase
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWR	interactive web-based response
JAK	Janus kinase
LBBB	left bundle branch block
LDL	low density lipoprotein
LFT	liver function test
LLOQ	lower limit of quantification
MAD	multiple ascending dose

Abbreviation	Term
MATE	multidrug and toxin extrusion
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDR	multi-drug resistance
MMP	matrix metallopeptidase
MMR	measles, mumps, rubella
MR	Modified release
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
msec	Millisecond
N/A	not applicable
NAb	neutralizing antibodies
NADPH	Nicotinamide adenine dinucleotide phosphate
NIMP	noninvestigational medicinal product
NOAEL	no-observed-adverse-effect level
OAT	organic anion transporter
OCT	organic cation transporter
PACL	Protocol administrative change letter
PASI	psoriasis area and severity index
PBMC	peripheral blood mononuclear cell
PCD	primary completion date
PCP	primary care physician
PCR	Polymerase chain reaction
PD	pharmacodynamic(s)
PFS	prefilled syringe
PGA	Physician Global Assessment
PI	principal investigator
PK	pharmacokinetic(s)
PP-NRS	peak-pruritus numerical rating scale
PPD	Purified Protein Derivative
PR	pulse rate
PRO	patient reported outcomes
PSI	psoriasis symptom inventory
PsO	psoriasis
PT	prothrombin time
CCI	[redacted]
PVC	premature ventricular contraction/complex
QD	once daily
QFT-G	QuantiFERON-TB Gold
QFT-GIT	QuantiFERON-TB Gold in Tube
QoL	quality of life

Abbreviation	Term
QT	Time from start of the Q wave to end of the T wave
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
QW	once weekly
qual	qualitative
RBC	red blood cell
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SBE	Single-blind extension
SC	subcutaneous
SCr	serum creatinine
CCI	[redacted]
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SSID	subject study identification number
SToD	study team on demand
SUSAR	suspected unexpected serious adverse reaction
t½	half life
TB	Tuberculosis
TBili	total bilirubin
TdP	torsade de pointes
TE	thromboembolic
TEAE	treatment emergent adverse events
T_{max}	time after administration of a drug when the maximum plasma concentration is reached
CCI	[redacted]
TYK	tyrosine-protein kinase
UC	Ulcerative colitis
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of normal
US	United States
Vss	steady state volume of distribution
CCI	[redacted]
WBC	white blood cell
WOCBP	woman of childbearing potential
W/W	weight for weight

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