A PHASE 2A, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, 16-WEEK STUDY EVALUATING THE SAFETY AND EFFICACY OF PF-06650833, PF-06700841, AND PF-06826647 IN ADULTS WITH MODERATE TO SEVERE HIDRADENITIS SUPPURATIVA

Investigational Product Number:	PF-06650833, PF-06700841, PF-06826647
Investigational Product Name:	Not Applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	CCI CCI CCI
European Clinical Trials Database (EudraCT) Number:	Not Applicable (N/A)
Protocol Number:	C2501007
Phase:	2a

Short Title: A 16-Week Study to Evaluate the Safety and Efficacy of PF-06650833, PF-06700841, and PF-06826647 in Adults With Hidradenitis Suppurativa

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Amendment 1	28 January 2020	• Schedule of Activities, Section 3 Objectives, Estimands, and Endpoints, and Section 8.1 Efficacy Assessments, added International Hidradenitis Suppurativa Severity Score System (IHS4). Rationale: IHS4 added to measure treatment effect. CCI [redacted] CCI [redacted] • Schedule of Activities, PK collection window added. Rationale: PK collection window added for clarity. • Schedule of Activities, Section 5.2 Exclusion Criteria, and Appendix 2 Clinical Laboratory Tests, Urine myoglobin testing added. Rationale: Urine myoglobin testing added to screening and reflex testing for CK >3 X ULN to ensure participant

		safety. • Schedule of Activities and Section 8.10 Patient Reported Outcome Measures, added footnote for PROs. Rationales: details added to provide clarity. • Schedule of Activities, Section 8.2.7 Suicidal Ideation and Behavior Risk Monitoring, Appendix 11 CSSRS, CSSRS will be performed at post-base line visits. Rationale: CSSRS added to post dose visits to ensure suicidal ideation and behavior will be evaluated during the study. • Schedule of Activities, and Appendix 2 Clinical Laboratory Tests, Urine analysis will be performed at central laboratory. Rationale: Urine analysis will be performed at central laboratory. Details added to provide clarity. • Section 3 Objectives, Estimands, and Endpoints, added new efficacy endpoints. Rationale: new secondary CCI [redacted] efficacy endpoints added to measure treatment effect by comparing of PF-06650833, PF-06700841, and PF-06826647 vs placebo. • Section 3 Objectives, Estimands, and Endpoints, CCI [redacted] CCI [redacted]

		CCI • Section 5.1 Inclusion Criteria, inclusion criterion #6 has been merged with #4. Rationale: requirements for the antibiotic therapy has been merged to provide clarity. • Section 5.1 Inclusion Criteria, inclusion criterion #5 added below text: Anti-TNF naïve; or Has initiated only one anti-TNF treatment including participants with inadequate response to the anti-TNF; Note: participants who initiated more than one anti-TNF treatments are not eligible. Rationale: details added to provide clarity. Anti-TNF naïve subjects are allowable. • Section 5.1 Inclusion Criteria and Section 5.3.4 Antiseptic therapy, allowable antiseptic washes are not limited. Rationale: language for allowable antiseptic washes are provided for flexibility. • Section 5.1 Inclusion Criteria, added definition for inadequate response of oral antibiotic. Rationale: added details for clarity. • Section 5.2 Exclusion Criteria, added following exclusions: History of recurrent (≥2) venous thrombosis or any arterial thromboembolism or known blood clotting disorders. Rationale: Subjects will be fully evaluated prior to study entry to ensure

		safety. • Section 5.2 Exclusion Criteria, exclusion criterion for hemoglobin has been revised from 11 to 9 g/dL. Rationale: there is no safety related effects on hemoglobin, the hemoglobin exclusion criterion was adjusted for HS population. C C I [redacted] Rationale: details modified to provide clarity. More information will be provided in a separate manual. • Section 9.1 Estimands and Statistical Hypotheses, some text deleted. Rationale: details will be provided in the statistical analysis plan. C C I [redacted] Rationale: details will be provided in the internal review committee charter. • Appendix 8 Guideline for Safety Monitoring and Discontinuation, retesting window has been updated to 1 week; added CK >3X ULN to monitoring criteria; hemoglobin criterion has been updated from 10 g/dL to 8 g/dL. CSSRS evaluation was added to discontinuation criterion. Rationale: retesting window updated to provide flexibility. CK >3X ULN will be re-tested to ensure safety. hemoglobin criterion was updated for HS population. CSSRS assessments will be performed during the study to

		ensure safety. • Appendix 10 eGFR calculation: added formula for cystatin C based eGFR. Rationale: formula added to provide clarity. • Appendix 10.4.4 Contraception Methods: added barrier method for female subjects randomized to receive PF-06650833/matching placebo who use implantable progestogen-only hormone contraception. Rationale: barrier method is added due to potential drug-drug interaction effect between PF-06650833 and progestogen. • Appendix 10.4.4 Contraception Methods: added restriction that all contraceptives containing ethinyl estradiol, being a CYP 1A2 inhibitor, are prohibited in female participants randomized to receive PF-06826647/matching placebo. Rationale: ethinyl estradiol is prohibited for female subjects randomized to receive PF-06826647/placebo due to potential drug-drug interaction effect. Minor administrative changes and sentence revisions made throughout the document.
Original protocol	16 August 2019	Not applicable (N/A)

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

TABLE OF CONTENTS

LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A 16-Week Study to Evaluate the Safety and Efficacy of PF-06650833, PF-06700841 and PF-06826647 in Adults With Hidradenitis Suppurativa.

Rationale

This multicenter, Phase 2a, randomized, double-blind, placebo controlled study is being conducted to provide data on safety, tolerability, pharmacokinetics (PK), and efficacy of PF-06650833, PF-06700841, and PF-06826647 in adults with moderate to severe hidradenitis suppurativa (HS). In addition, the study is intended to provide additional information for determining the future clinical development of janus kinase (JAK) inhibitors and/or IL-1 receptor associated kinase 4 (IRAK4) in HS.

Objectives, Estimands, and Endpoints

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
To evaluate the efficacy of PF-06650833, PF-06700841, and PF-06826647 vs placebo in participants with HS as assessed by HiSCR.	Percentage of participants with HiSCR response* at Week 16.	This estimand uses a composite estimand theory (ICH E9 addendum) and is intended to provide a population level estimate of the treatment effect of the IP on a binary endpoint regardless of participant compliance with the IP dosing. Population-level summary: difference between treated and placebo in proportion of participants with HiSCR response at Week 16.
Secondary:	**Secondary:**	**Secondary:**
To evaluate the efficacy of PF-06650833, PF-06700841, and PF-06826647 vs placebo in participants with HS at Week 16 and over time.	Percentage of participants with HiSCR response* at Weeks 1, 2, 4, 6, 8, and 12. Percentage of participants with a total abscess and inflammatory nodule (AN) count of 0 or 1; 0, 1, or 2 at Week 16.	This estimand is intended to provide a population level estimate of the treatment effect of the IP on a binary endpoint regardless of participant compliance with the IP dosing. Population-level summary: difference between treated and placebo in proportion of participants with HiSCR response at Weeks 1, 2, 4, 6, 8 and 12, respectively; difference between treated and placebo in proportion of participants with a total AN count of 0 or 1, or 0, 1 or 2, respectively at

	Percent change from baseline (CFB) in AN count at Weeks 1, 2, 4, 6, 8, 12 and 16.	Week 16. This estimand is intended to provide a population level estimate of the treatment effect of the IP on a continuous endpoint regardless of participant compliance with the IP dosing. Population-level summary: difference between treated and placebo change from baseline in AN count at Weeks 1, 2, 4, 6, 8, 12 and 16.
To evaluate the efficacy of PF-06650833, PF-06700841, and PF-06826647 vs placebo on International Hidradenitis Suppurativa Severity Score System (IHS4).	Absolute score and percent CFB in IHS4 at Weeks 1, 2, 4, 6, 8, 12 and 16.	This estimand is intended to provide a population level estimate of the treatment effect of the IP on a continuous endpoint regardless of participant compliance with the IP dosing. Population-level summary: difference between treated and placebo in absolute score and change from baseline on IHS4 at Weeks 1, 2, 4, 6, 8, 12 and 16.
To evaluate the effects of PF-06650833, PF-06700841, and PF-06826647 vs placebo on HS flare.	Proportion of participants who experience an HS flare, defined as at least a 25% increase in AN count with a minimum increase of 2 relative to Baseline, at Weeks 4, 8, 12 and 16.	The estimand is intended to provide a population level estimate of the treatment effect of the IP on a binary endpoint regardless of participant compliance with IP dosing. Population-level summary: difference between treated and placebo in proportion of participants experience flare at Weeks 4, 8, 12 and 16.
To evaluate the efficacy of PF-06650833, PF-06700841, and PF-06826647 vs placebo on pain and pain reduction over time in participants with HS.	Percentage of participants with ≥30% reduction and ≥1-unit reduction from baseline in PGA-Skin Pain numeric rating scale (NRS30) – at worst and on average, respectively, amongst participants with baseline NRS ≥3, at Weeks 1, 2, 4, 6, 8, 12 and 16. Percent CFB in NRS, at worst and on average respectively, in participants who have baseline NRS ≥3, at Weeks 1, 2, 4, 6, 8, 12 and 16.	This estimand is intended to provide a population level estimate of the treatment effect of the IP on a binary endpoint regardless of participant compliance with the IP dosing. Population-level summary: difference between treated and placebo in proportion of participants with ≥30% reduction and ≥1-unit reduction from baseline in PGA-Skin Pain NRS (NRS30), at worst and on average, respectively, amongst participants with baseline NRS ≥3, at Weeks 1, 2, 4, 6, 8, 12 and 16.

	CFB in NRS, at worst and on average respectively, at Weeks 1, 2, 4, 6, 8, 12 and 16.	This estimand is intended to provide a population level estimate of the treatment effect of the IP on a continuous endpoint regardless of participant compliance with the IP dosing. Population-level summary: difference between treated and placebo percent change from baseline in NRS, at worst and on average respectively, in participants who have baseline NRS ≥3, at Weeks 1, 2, 4, 6, 8, 12 and 16. Difference between treated and placebo change from baseline in NRS, at worst and on average respectively, at Weeks 1, 2, 4, 6, 8, 12 and 16.
To evaluate the efficacy of PF-06650833, PF-06700841, and PF-06826647 vs placebo on erythema.	Proportion of participants achieving erythema score of 1 or 0 in all affected anatomic regions among participants who have an erythema score of 2 or more in at least 1 anatomic region at baseline.	The estimand is intended to provide a population level estimate of the treatment effect of the IP on a binary endpoint regardless of participant compliance with IP dosing. Population-level summary: difference between treated and placebo in proportion of participants achieving erythema score of 1 or 0 in all affected anatomic regions among participants who have erythema score of 2 or more in at least 1 anatomic region at baseline.
To assess the safety and tolerability of PF-06650833, PF-06700841, and PF-06826647 vs placebo in participants with HS.	Incidence of TEAEs (AEs and SAEs), significant changes in vital signs, clinical laboratory abnormalities, and ECG.	There is no defined estimand for these endpoints and they will be analyzed using Pfizer data standards as applicable.
To evaluate the effects of PF-06650833, PF-06700841, and PF-06826647 vs placebo on patient centered outcomes in participants with HS.	Absolute score and CFB at time points specified in the SoA in HS Symptom Items and Dermatology Life Quality Index (DLQI) total score. Proportion of participants achieving a DLQI=0 or 1.	These endpoints will be analyzed descriptively and with respect to an estimand.
To evaluate the PK of PF-06650833, PF-06700841, and PF-6826647 vs placebo in participants with HS.	Summary of plasma concentration of PF-06700841, PF-06826647 and PF-06650833.	There is no defined estimand for these endpoints and they will be analyzed using Pfizer data standards as applicable.


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*HiSCR requires:

- At least a 50% reduction in the total AN count relative to baseline; and
- No increase in abscess count; and
- No increase in draining fistula count.

For all endpoints, baseline is defined as the result closest prior to dosing on Day 1.

Overall Design

This is a Phase 2a, randomized, double-blind, placebo-controlled, parallel group, multicenter platform study with 3 kinase inhibitors (PF-06650833, PF-06700841 and PF-06826647) in participants with moderate to severe HS. The study will have a maximum duration of approximately 26 weeks. This includes an up to 6-week Screening Period, a 16-week Dosing Period and a 4-week Follow-up Period. The study will not be blinded across the PF-06650833, PF-06700841 and PF-06826647 treatment arms, but will be placebo-controlled double-blinded within each investigational product (IP) treatment arm.

Following the screening period, participants who meet eligibility criteria at the baseline visit, will be randomly assigned to receive PF-06650833 or matching placebo in a 3:1 ratio, or PF-06700841 or matching placebo in a 3:1 ratio, or PF-06826647 or matching placebo in a 3:1 ratio. One oral dose level of each PF-06650833 (400 mg QD), PF-06700841 (45 mg QD) and PF-06826647 (400 mg QD) or matching placebo will be investigated. No more than 30% of enrolled participants will be inadequate anti-tumor necrosis factor (TNF) responders. Participants will be stratified according to whether they are an inadequate anti-TNF responder or not.

Additionally, no more than 20% of enrolled participants may enter the study on a background of concomitant oral antibiotic therapy for treatment of HS; the dosing regimen (dose and frequency) must have been stable for at least 8 weeks (56 days) prior to the baseline (Day 1) visit and must remain stable throughout study participation. Participants will be stratified according to whether they are on a background of concomitant antibiotic therapy or not.

Biopsies of unaffected areas and lesional area biopsies will be collected from participants at selected sites; it is expected that approximately 60 participants across these selected sites will have biopsies collected.

Number of Participants

The study will enroll a total of approximately 192 participants (expected to provide approximately 156 completers). The study will be conducted globally at approximately 60 study sites.

Intervention Groups and Duration

Following the screening period, participants who meet eligibility criteria at the baseline visit, will be randomly assigned to receive PF-06650833 (400 mg QD) or matching placebo in a 3:1 ratio, PF-06700841 (45 mg QD) or matching placebo in a 3:1 ratio, or PF-06826647 (400 mg QD) or matching placebo in a 3:1 ratio.

Intervention Name	PF-06650833	PF-06700841	PF-06826647
ARM Name	PF-06650833 400 mg Active and Placebo	PF-06700841 45 mg Active and Placebo	PF-06826647 400 mg Active and Placebo
Dose Formulation	Tablet	Tablet	Tablet
Unit Dose Strength(s)	200 mg Active Placebo	25 mg, 5 mg Active Placebo	100 mg Active Placebo
Dosage Level(s)	400 mg QD	45 mg QD	400 mg QD
Route of Administration	Oral	Oral	Oral
Packaging and Labeling	CCI [redacted]	CCI [redacted]	CCI [redacted]
Current/Former Name(s) or Alias(es)	IRAK4	TYK2/JAK1	TYK2

CCI [redacted]

[redacted]

Statistical Methods

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

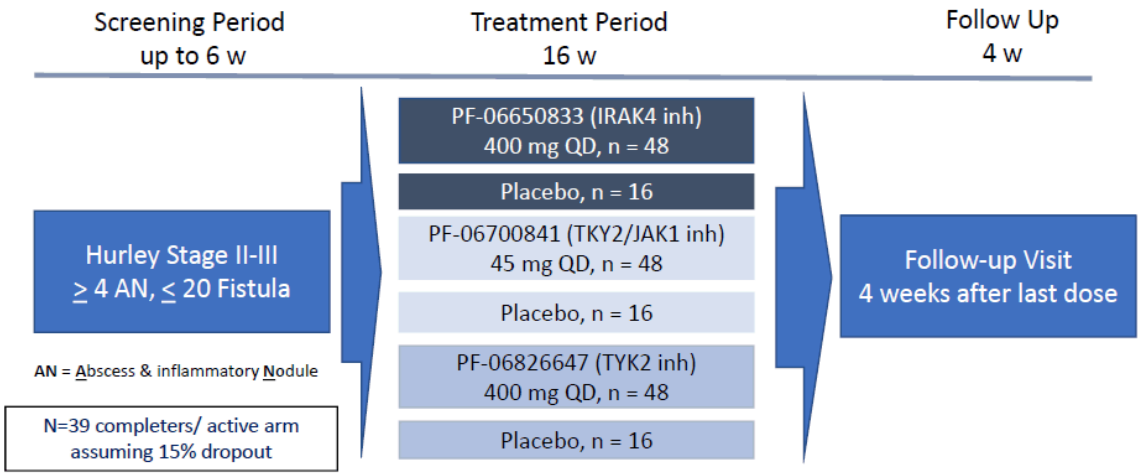
The primary estimand will be the population treatment effect on proportion of participants with hidradenitis suppurativa clinical response (HiSCR) at Week 16 for the active treatment group relative to placebo without regard to IP compliance.

Hidradenitis suppurativa clinical response, the primary endpoint used, is defined as:

- At least a 50% reduction in the total abscess and inflammatory nodule (AN) count relative to baseline; **and**
- No increase in abscess count; **and**
- No increase in draining fistula count.

Sample size calculation is based on the primary endpoint of HiSCR response at 16 weeks. A total of approximately 192 participants will be randomized in 3 active treatment groups (48/arm) and 3 placebo groups (16/arm) to have 39 completers for each active treatment arm, assuming a 15% dropout rate and the active treatment arm HiSCR response rate of 60% and placebo HiSCR rate of 30%. Statistical comparisons will be made between each of the active treatment arms against the 3 placebo groups pooled together. With one-sided family-wise error rate of 0.1 with a Bonferroni correction (0.033 after Bonferroni adjustment for 3 comparisons), this sample size will provide approximately 80% power. No statistical comparisons will be done between active treatment arms.

1.2. Schema



1.3. Schedule of Activities (SoA)

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

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

Study Procedure	**Screening**	**Baseline**	**Investigational Treatment Period**							**Follow-Up (EOS)**	**Early Termination[b]**
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Week	**-6 to -1**	**Day 1**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**ET**
Study Day[a]	**-42 to -1**	**1**	**8**	**15**	**29**	**43**	**57**	**85**	**113**	**141**	**ET**
Visit Window (Days)	**N/A**		**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	
Enrollment Procedures											
Informed consent	X										
Medical history & demography	X	X									
Eligibility assessment	X	X									
Medication History	X	X									
Randomization		X									
Clinical Assessments											
Full Physical Exam	X	X							X		X
Brief Physical Exam			X	X	X	X	X	X		X	
Vital signs[c]	X	X	X	X	X	X	X	X	X	X	X
ECG[d]	X	X[d]			X		X[d]	X	X[d]		X
Height/Weight[e]	X	X							X		
Chest radiograph[f]	X										
C-SSRS[g]	X						X		X		
Laboratory Assessments											
Hematology/Blood chemistry (including eGFR)	X	X	X	X	X	X	X	X	X	X	X
Urine myoglobin[v]	X										
Serum cystatin C		X	X	X	X	X	X	X	X	X	X
Lipid panel[h] (fasting)		X					X		X		
Urinalysis (to be processed at central lab)[i]	X	X	X	X	X	X	X	X	X	X	X
FSH[j]	X										

Study Procedure	Screening	Baseline	Investigational Treatment Period							Follow-Up (EOS)	Early Termination[b]
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Week	**-6 to -1**	**Day 1**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**ET**
Study Day[a]	**-42 to -1**	**1**	**8**	**15**	**29**	**43**	**57**	**85**	**113**	**141**	**ET**
Visit Window (Days)	**N/A**		**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	
Serum β-HCG[k]	X										
Urine β-HCG[l] (done at site)		X	X	X	X	X	X	X	X	X	X
HIV serology (per local regulations)	X										
HBsAg, HBcAb, and HCVAb (Hep B and Hep C reflex testing)[m]	X										
Tuberculosis test	X										
Urine drug screening	X										
Pharmacokinetics (PK)											
PK pre-dose		X	X	X	X	X	X	X	X		
PK 0.5, 1, 2, 4 hours post dose							X[w]				
PK sample											X[w]
Banked Biospecimens and Pharmacodynamics (PD)											
CCI [redacted]		[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]
Study Treatment											
IP dispensing[o]		X			X		X	X			
IP accountability			X	X	X	X	X	X	X		X
Clinical Assessments of HS											
Hurley Stage	X	X						X	X		X
Lesion Counts[p]	X	X	X	X	X	X	X	X	X		X
Abscess Count	X	X	X	X	X	X	X	X	X		X
Inflammatory Nodule Count	X	X	X	X	X	X	X	X	X		X
Fistula Count	X	X	X	X	X	X	X	X	X		X
Erythema Assessments[q]	X	X	X	X	X	X	X	X	X		X
CCI [redacted]	[redacted]	[redacted]						[redacted]	[redacted]		[redacted]
IHS4 Score	X	X	X	X	X	X	X	X	X		X
Patient Reported Outcomes (PROs)[r]											
Dispense eDiary device and instructions on use	X										

Study Procedure	Screening	Baseline	Investigational Treatment Period							Follow-Up (EOS)	Early Termination[b]
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Week	**-6 to -1**	**Day 1**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**ET**
Study Day[a]	**-42 to -1**	**1**	**8**	**15**	**29**	**43**	**57**	**85**	**113**	**141**	**ET**
Visit Window (Days)	**N/A**		**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	
Patient Global Assessment of Skin Pain (Numeric Rating Scale)[s]	X	→	→	→	→	→	→	→	→	X	X
HS Symptom Items[s]	X	→	→	→	→	→	→	→	→	X	X
CCI											
DLQI		X			X		X	X	X	X	X
CCI											
Other											
CCI											
Monitoring											
Contraception Check[u]	X	X	X	X	X	X	X	X	X	X	X
Prior/Concomitant Treatment(s)	X	→	→	→	→	→	→	→	→	→	X
AE monitoring	X	→	→	→	→	→	→	→	→	→	X

Abbreviations: AE= adverse event; C-SSRS= Columbia Suicide Severity Rating Scale; EOS = end of study; CCI ;
DLQI= Dermatology Life Quality Index; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; CCI ;
FSH= follicle stimulating hormone; β-HCG= human chorionic gonadotropin; HBsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibody;
HCVAb = hepatitis C virus antibody; HIV= human immunodeficiency virus; IHS4 = International Hidradenitis Suppurativa Severity Score System;
IP = Investigational Product; PE= physical exam; CCI ;
PK = pharmacokinetic; PRO = patient reported outcome; CCI
VAS = visual analog scale; WOCBP= women of child-bearing potential; → = daily assessment.

a. Days relative to Day 1.

b. Participants who prematurely withdraw during Investigational Treatment Period should return for an Early Termination (ET) visit and enter into Follow-up with their EOS Visit occurring approximately 4 weeks after their ET Visit.

c. Vital signs consist of blood pressure, pulse rate, and temperature and should be performed before laboratory blood collection and after 5 minutes rest while supine. Participants should not use nicotine containing products or ingest caffeine 30 minutes prior to blood pressure and pulse rate measurements.

d. 12-lead ECG should be performed after the participant has rested quietly for at least 10 minutes in a supine position and before laboratory blood collection (except for the pose dose ECG). On Weeks 8 and 16 single ECGs will be collected prior to dosing and also at 2 hours (with a ±15 minutes window) post dose. Refer to Section 8.2.4 for details.

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

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

g. Use C-SSRS "Lifetime" version at Screening. Participants who have recent or active suicidal ideation or behaviors will be excluded from study entry. Use C-SSRS "post base line visits" version for Week 8 and 16 Visits.

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

i. Collect urine sample for central laboratory urinalysis and urine microscopy at Screening and pre-dose at Baseline. At postdose visits: urine microscopy is indicated if the urinalysis is positive for blood, nitrite, leukocyte esterase and/or protein, or there is clinical suspicion of urinary tract infection, or decrease in renal function; urine culture is performed if urinalysis is positive for nitrite and/or leukocyte esterase, or if otherwise clinically indicated.

j. To be done in females 60 years or older and who are amenorrheic for at least 12 consecutive months.

k. Required for WOCBP at Screening.

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

m. Reflex-testing (if necessary) consists of: participants at Screening who are HBsAg negative but HBcAb positive should be reflex-tested for HBsAb, if HBsAb is positive, may enroll; if HBsAb is negative, they will be screen-failed; participants at Screening who are positive for HCV Ab will be reflex-tested for HCV RNA and, if HCV RNA is negative, may enroll; if HCV RNA is positive, they will be screen-failed.

C [redacted]

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

p. Refer to Section 8.1.1.1 for details of measurements.

q. At every visit, for each affected anatomic region, the investigator will assess the overall degree of erythema using a four-point ordinal scale ranging between 0 and 3.

r. Effort should be made to complete all PRO questionnaires before any other assessments (except that PGA Skin Pain NRS and HS Symptoms will be completed daily at home). PGA Skin Pain NRS and HS Symptoms will be completed as a daily diary from Day -7 prior to Baseline and through Week 16 at home, and at site at the FU visit and the ET visit (if applicable). At site visits participants will complete PROs in the following order: CCI [redacted] DLQI, CCI [redacted]. At all other times not associated with site visits, participants will complete PROs in the following order: PGA Skin Pain NRS and HS Symptom Items.

s. PGA Skin Pain NRS and HS Symptoms Items will be completed daily from Day -7 throughout Week 16 at home. Both will be completed at the site at the follow-up visit and at the early termination visit (if applicable).

c [redacted]

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

v. Urine myoglobin will be measured at Screening and in case of CK >3 x ULN during the study.

w. PK collection windows are defined as follows (if applicable): ±15 minutes for 0.5 hour post dose; +30 minutes for 1 hour post dose; ±30 minutes for 2 and 4 hours post dose. Blood sample for PK will be collected at early termination visit for subjects who discontinue early from the Treatment Period only if the most recent dose taken prior to ET visit was within 48 hours.

2. INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, inflammatory, recurrent, debilitating skin disease that usually presents after puberty with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body.[1] HS presents a variable clinical course. One of the main features of the disease is the intertriginous occurrence, although, other areas of skin may also be affected. The affected areas are in decreasing order of frequency: inguinal, axillary, perineal and perianal as well as the submammary and/or intermammary fold in women, buttocks, mons pubis, scalp, area behind the ears and eyelids.

The prevalence of self-reported disease is about 1% in Western Europe. The average interval from the onset of symptoms to diagnosis is 7.2 years. Women are affected 2 to 5 times as frequently as men, and the disease may be more common in blacks than in whites. Disease severity ranges from mild (localized lesions) to severe (multiple areas of widely dispersed lesions, including interconnected sinus tracts and hypertrophic scars). Pain, drainage, and range-of motion limitations from scarring can decrease the quality of life.[2,3]

Pain is a prominent feature of HS, which is reflected in the recently defined set of core outcomes to be assessed in future trials.[4,5] The majority of patients rated their pain on a Numerical Rating Scale-11 (NRS-11) ranging from 4/10 - 10/10 and described it at various times as hot, burning, pressure stretching, cutting, sharp, taut, splitting, gnawing, pressing sore, throbbing, and aching.[6]

The pathophysiology of HS remains incompletely defined. Numerous inflammatory mediators including tumor necrosis factor (TNF)-α, interleukin (IL)-17, IL-32 and IL-36 subtypes have been implicated in the disease. However, there is an incomplete understanding of the source and triggers of these mediators and how they sustain the chronic inflammation that characterizes this disease.[7]

The severity of HS is classified in stages according to Hurley definition:

- Hurley Stage I: Abscess formation, single or multiple, without sinus tracts and cicatrization.
- Hurley Stage II: Recurrent abscesses with tract formation and cicatrization, single or multiple, widely separated lesions.
- Hurley Stage III: Diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across the entire area.

Stage I disease is most common (68% of patients), while stage II occurs in 28% of patients, and 4% of HS patients have stage III.[1]

The European S1 HS guideline suggests that the disease should be treated based on its individual subjective impact and objective severity. Locally recurring lesions can be treated by classical surgery or light amplification by stimulated emission of radiation (LASER) techniques, whereas medical treatment either as monotherapy or in combination with radical surgery is more appropriate for widely spread lesions. Medical therapy may include antibiotics (clindamycin plus rifampicin, tetracyclines), acitretin and biologics (adalimumab, infliximab). Adjuvant measurements, such as pain management, treatment of superinfections, weight loss and tobacco abstinence have to be considered.[1]

Currently adalimumab is the only approved medical treatment for moderate to severe HS. It is based on two similarly designed (PIONEER I and PIONEER II), Phase 3 multicenter trials of adalimumab for HS.[3] A total of 307 patients were enrolled in PIONEER I, and 326 were enrolled in PIONEER II. Clinical response rates [hidradenitis suppurativa clinical response (HiSCR)]: defined as at least a 50% reduction from baseline in the abscess and inflammatory-nodule count, with no increase in abscess or draining-fistula counts] at Week 12 were significantly higher for the groups receiving adalimumab weekly than for the placebo groups: 41.8% versus 26.0% in PIONEER I ($P = 0.003$) and 58.9% versus 27.6% in PIONEER II ($P<0.001$). Patients receiving adalimumab had significantly greater improvement than the placebo groups in rank-ordered secondary outcomes (lesions, pain, and the modified Sartorius score for disease severity) at Week 12 in PIONEER II only.[3] The main difference between the study designs is that in PIONEER I, patients receiving oral antibiotic agents for HS were required to stop treatment for at least 28 days before baseline; in PIONEER II, patients were allowed to continue treatment with antibiotics (tetracycline class) in stable doses.

Thus, a significant number of patients (~40%) with moderate to severe HS did not respond to treatment with adalimumab, and therefore there is still an unmet need for an effective, safe, and well tolerated treatment in patients with moderate to severe HS.

The objectives of the current study are to evaluate the efficacy, safety and tolerability of PF-06650833, an IL-1 receptor associated kinase 4 (IRAK4) inhibitor, PF-06700841, a dual inhibitor of human tyrosine kinase 2 (TYK2) and Janus kinase 1 (JAK1), and PF-06826647, a potent TYK2 inhibitor, in patients with moderate to severe HS. Since the pathophysiology of HS is not defined completely, it is uncertain which of these three disease targets and pathways would be of more relevance for the treatment of patients with HS. Therefore, the additional objective of this study is to compare the efficacy of PF-06650833, PF-06700841, and PF-06826647 with the goal to select one of these inhibitors for further clinical development.

PF-06650833 is currently being investigated in rheumatoid arthritis and will be investigated in HS.

PF-06700841 is currently being investigated in patients with plaque psoriasis (PsO), alopecia areata (AA), ulcerative colitis, Crohn's disease, vitiligo, and will be investigated in HS.

PF-06826647 is being investigated in participants with plaque PsO and will be investigated in HS.

2.1. Study Rationale

This multicenter, Phase 2a, randomized, double-blind, placebo controlled study is being conducted to provide data on safety, tolerability, pharmacokinetics (PK), and efficacy of PF-06650833, PF-06700841, and PF-06826647 in adults with moderate to severe HS. In addition, the study is intended to provide additional information for determining the future clinical development of JAK inhibitors and/or IRAK4 in HS.

2.2. Background

The following sections summarize available in vitro and in vivo human disposition and drug-drug interaction profiling for PF-06650833, PF-06650833, PF-06700841 and PF-06826647 as well as the available clinical safety and pharmacology of these investigational products. Further details of can be found in the individual Investigator Brochures (IB).

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2.2.2. Nonclinical Safety of PF-06650833

Nonclinical toxicity studies with PF-06650833 were conducted using a sprayed dried dispersion (SDD) or nanomilled formulation. Since exposures with the SDD formulation were higher than those observed with the same dose using the nanomilled formulation, toxicity findings are presented in terms of exposure, instead of dose. In safety pharmacology studies, PF-06650833-related increases in heart rate and decreases in blood pressure (BP) were observed in telemetered rats and dogs [at maximum observed concentration (C_{max}) ≥358 ng/mL and area under the curve at 24 hours (AUC_{24}) ≥1540 ng•h/mL]. Although the hERG IC_{50} was >100 µM (36,100 ng/mL), small (+6 to +11 msec) prolongations of the QTc interval was observed in the 24-day cardiovascular (CV) study in telemetered dogs (at C_{max} ≥742 ng/mL and AUC_{24} ≥8550 ng•h/mL).

PF-06650833 was evaluated in single-dose and exploratory toxicity studies in rats (7 or 14 days) and dogs (14 days) using both the SDD and nanomilled formulations, and was evaluated Good Laboratory Practice (GLP) toxicity studies up to 26 weeks duration in rats and up to 39 weeks duration in dogs, using the nanomilled formulation. In these studies, the renal system, heart, skeletal muscle, liver, and the gastrointestinal (GI) tract were identified as PF-06650833-related target organs.

PF-06650833-related and adverse, mild to severe obstructive nephropathy occurred in the 3-month study in rats (at C_{max} ≥2910 ng/mL and AUC_{24} ≥18,300 ng•h/mL), that was still observed at the end of the 1-month recovery period in female rats. However, obstructive nephropathy was not observed at any dose tested in the 26-week study in rats (at C_{max} ≤3360 ng/mL and AUC_{24} ≤34,400 ng•h/mL). Urine sediment crystals (determined to be PF-06650833 or its metabolites) were observed in rats at C_{max} ≥1080 ng/mL and AUC_{24} ≥5920 ng•h/mL. Following 8-week to 1-month recovery phases in the 3-month and 26-week studies, respectively, no crystals in urine sediment were observed. At very high exposures, PF-06650833-related pale kidney, renal tubular dilatation, and pelvic inflammation was observed in exploratory studies in rats (at C_{max} = 7640 ng/mL and AUC_{24} = 33,500 ng•h/mL) and congestion of the medulla secondary to PF-06650833-related toxicity was observed in dogs (at C_{max} ≥7460 ng/mL and AUC_{24} ≥35,100 ng•h/mL).

The no observed adverse effect level (NOAEL) for PF-06650833 when administered by oral gavage for 26 weeks in rats or 39 weeks in dogs was 150 mg/kg/day in female rats (C_{max}=3360 ng/mL and AUC_{24}=34,400 ng•h/mL), 300 mg/kg/day in male rats (C_{max}=1780 ng/mL and AUC_{24}=15,800 ng•h/mL), and 60 mg/kg/day (30 mg/kg twice daily (BID), 7 hours apart) in dogs (C_{max}=1710 ng/mL and AUC_{24}=17,200 ng•h/mL).

PF-06650833 was negative for mutagenicity in bacterial reverse mutation assays. PF-06650833 did not induce micronuclei in vivo, in polychromatic erythrocytes in peripheral blood of rats, at any dose tested. PF-06650833 absorbs in the Ultra Violet A (UVA) range but was not phototoxic in an in vivo assay.

In the fertility and early embryonic development study in rats, there were no PF-06650833 related effects on male or female reproductive and early embryonic toxicity; therefore the NOAEL was 1000 mg/kg/day (mean plasma concentrations of 2257 and 3457 ng/mL for males and females, respectively), the highest dose tested. In the embryo-fetal developmental (EFD) study in rats, PF-06650833-related fetal skeletal malformations and variations occurred at C_{max} 5020 ng/mL and AUC_{24} 42,600 ng•h/mL. The maternal NOAEL in rats was 1000 mg/kg/day and the developmental NOAEL in rats was C_{max}=3560 ng/mL and AUC_{24}=20,000 ng•h/mL (100 mg/kg/day). There was no maternal or developmental toxicity in the EFD study in rabbits, therefore the maternal and developmental NOAEL was 1000 mg/kg/day (C_{max}=2030 ng/mL and AUC_{24}=25,600 ng•h/mL), the highest dose tested.

Further details on the nonclinical safety program of PF-06650833 are provided in the current PF-06650833 IB.

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More detailed information on the clinical PK with PF-06650833 can be found in the current PF-06650833 IB.

2.2.5. Nonclinical Pharmacokinetics and Metabolism of PF-06700841

In vitro and in vivo metabolite profiling indicated that the primary clearance mechanisms for PF-06700841 were through CYP-mediated oxidation. In vitro studies using human hepatocytes indicated greater than 88% of the PF-06700841 metabolism observed was attributed to CYP450, with CYP3A4 identified as the major contributor (~62%). In vitro studies indicated that PF-06700841 showed a low risk of inhibiting the major drug metabolizing CYP or UGT enzymes, as well as a low risk of significant induction of CYP3A4, 2B6, or 1A2. PF-06700841 was shown to be a substrate for MDR1, but not BCRP, OATP1B1, or OATP1B3. PF-06700841 showed a low risk of inhibition of bile salt export pump (BSEP), OAT1, OAT3, OATP1B1, OATP1B3. However, PF-06700841 showed potential to inhibit BCRP, MDR1, OCT1, OCT2, MATE1, and MATE2K. Clinically, PF-06700841 was shown to increase serum creatinine (SCr) levels (OCT2 substrate), but not cystatin C.

2.2.6. Nonclinical Safety of PF-06700841

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, non-adverse, target organs identified include the immune and hematolymphopoietic systems (thymus, spleen, lymph nodes, and bone marrow), cardiovascular system (BP, heart rate, corrected Q wave interval [QTc]), GI 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 non-pregnant rabbits.

In oral EFD studies in rats and rabbits, adverse PF-06700841-related developmental effects occurred in rats only (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 of PF-06700841 are provided in the current PF-06700841 IB.

2.2.7. Clinical Safety of PF-06700841

The first in human (FIH) study was a Phase 1, randomized, double-blind, third party open, placebo-controlled, single and multiple dose escalation, parallel group study in healthy adult participants and participants with plaque PsO, with a relative bioavailability (BA) and food effect assessment of a tablet formulation of PF-06700841 in healthy adult participants. In the completed FIH study (B7931001), 41 healthy volunteers were exposed to single doses and 26 of the 41 participants received multiple daily doses of PF-06700841 over 10 days; a small cohort of plaque PsO patients (n=21) were treated QD with PF-06700841 for 28 days at 30 mg and 100 mg doses.

An additional healthy volunteer cohort was included to support the evaluation of the relative BA of a tablet formulation of PF-06700841, and assessment of a high fat meal on tablet BA. Twelve healthy participants participated in this BA assessment, and received single doses of open label PF-06700841 in a 3-way cross over design (PF-06700841 tablet fasted, PF-06700841 solution/suspension fasted, and PF-06700841 tablet under fed conditions). PF-06700841 was generally safe and well tolerated in the Phase 1 clinical study B7931001.

A Phase 1 study to determine the absorption, distribution, metabolism, and excretion (ADME) of PF-06700841 (B7931014) in healthy males is ongoing.

The most commonly reported all causality TEAEs across active participants in both single ascending dose (SAD) and multiple ascending dose (MAD) cohorts were increased blood creatinine, and decreased neutrophil count. In the SAD period, 1 participant in the PF-06700841 100 mg group had SCr values meeting the criteria for high levels [>1.3 X upper limit of normal (ULN)]. In the MAD period, 4 participants (1, 2, and 1 participants in the PF-06700841 10 mg QD, 100 mg QD, and 50 mg BID groups, respectively) had SCr values meeting the criteria for high levels. No participants in the PsO period had SCr values meeting the criteria for high levels. In the SAD period, 3 participants (1 participant each in the PF-06700841 1 mg, 200 mg, and placebo group) had abnormal low neutrophil counts (<0.8 X LLN). In the MAD period, 14 participants (1, 3, 3, 5, and 2 participants in the PF-06700841 10 mg QD, 100 mg QD, 50 mg BID, 175 mg QD, and placebo group, respectively) had abnormal low neutrophil counts. In the PsO period, 6 participants (1 and 5 participants in the PF-06700841 30 mg and 100 mg QD groups, respectively) had abnormal low neutrophil counts. All laboratory abnormalities reported as

AEs were mild in severity, except for one case of neutropenia which was reported as moderate in severity (Grade 3 neutropenia). No neutrophil counts reached or fell below 500 cells/mm^3 during the study.

The most commonly reported all causality TEAEs across active participants in the PsO cohorts treated with either 30 mg or 100 mg PF-06700841 were blood creatinine increased and neutrophil count decreased.

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

In the BA cohort, the reported AEs were nausea, contusion, and headache, each of which was experienced by 1 participant. All TEAEs were mild in severity.

Oral administration of PF-06700841 at multiple doses of 100 mg QD was well-tolerated and generally safe in healthy Japanese participants investigated in study B7931009. There were no deaths, SAEs, severe AEs, discontinuations due to AEs, or dose reductions or temporary discontinuations due to AEs during this study.

Overall, 3 TEAEs were reported by 1 participant following placebo treatment, including palpitations, abdominal pain and insomnia. Among these AEs, palpitations and insomnia were considered treatment-related. Seven (7) TEAEs were reported by 3 participants following oral administration of PF-06700841 100 mg, including flatulence, fatigue, viral upper respiratory tract infection, headache, somnolence, nocturia and haematoma. Among these AEs; flatulence, headache, somnolence and nocturia were considered treatment-related by the investigator. One (1) AE of abdominal pain in the placebo treatment group was moderate and the others were considered mild in severity.

There were no clinically significant findings observed in laboratory parameters, vital signs, ECG parameters, and physical examinations.

PF-06700841 was administered to 6 healthy Japanese participants in the Phase 1 study B7931009 at a daily dose of 100 mg. PF-06700841 demonstrated acceptable safety and tolerability in healthy Japanese participants investigated in study B7931009, in which multiple doses of 100 mg QD or placebo was administered for 10 days. There were no deaths, SAEs, severe AEs, discontinuations due to AEs, or dose reductions or temporary discontinuations due to AEs during this study. All AEs were mild or moderate in severity. An AE of palpitations was observed in a placebo participant during the treatment period. There were no clinically significant findings observed in laboratory parameters, vital signs, ECG parameters, and physical examinations.

In study B7931019, a definitive QT study for PF-06700841 in healthy participants, each participant received single oral doses of PF-06700841 200 mg, placebo and moxifloxacin 400 mg in a 3-way crossover design. Treatment assignments to PF-06700841 and placebo were blinded to participants and investigator but moxifloxacin treatment was unblinded. In total, 33 participants were enrolled with 32 completed all 3 treatments. Overall, PF-06700841 200 mg and moxifloxacin 400 mg were safe and well tolerated with no deaths, SAEs, severe AEs or discontinuation due to AEs. A total of 24 TEAEs (all causalities) were reported in 15 participants after PF-06700841 treatment. There were 11 and 12 TEAEs reported in 10 and 8 participants after moxifloxacin and placebo treatment respectively. All AEs were mild to moderate in severity. Despite QTc increases observed after single doses of PF-06700841 200 mg and moxifloxacin 400 mg, there were no clinically significant findings in ECG categorical analyses including no changes in corrected QT (Fridericia method) (QTcF >60) msec or an absolute value >500 msec.

PF-06700841 was also investigated in patients with plaque PsO (B7931004). This study was a Phase 2a, randomized, double-blind, placebo-controlled, parallel group, multicenter study in adult participants with moderate to severe plaque PsO. The first part of the study, following a screening period (up to 6 weeks), was a 4-week induction period with double-blind daily treatment. At the end of Week 4, all participants switched to their predefined double-blind maintenance treatment regimen for Week 5 through Week 12. A total of 212 PsO participants were randomized and received at least one dose of study treatment. The randomization ratio was 7:1, active:placebo.

During the first 4 weeks of the treatment period, participants received 1 of the 3 treatments orally, either 30 mg QD or 60 mg QD of PF-06700841, or matching placebo. During the 8-week maintenance portion of the treatment period (Weeks 5 through 12), participants received 1 of the 4 treatments, either PF-06700841 10 mg, or 30 mg QD, or a 100 mg once weekly (QW) regimen of PF-06700841, or matching placebo. Maintenance dose level and regimen were assigned at the initial time of randomization into the study. All participants, regardless of assigned regimen (ie, QD or QW) received blinded QD tablets throughout the study treatment period to maintain the study blind.

The proportion of participants with all-causality 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 the treatment groups experienced mild or moderate all-causality TEAEs, and only 11 (5.2%) out of 212 participants experienced severe all-causality TEAEs. Overall, there were no dose-dependent increases in the all-causality TEAEs.

A total of 13 participants discontinued from the study due to TEAEs. One participant in the 60 mg QD to placebo group discontinued the investigational product treatment, but remained in the study. There were 5 participants with dose reduced or temporarily discontinued due to AEs.

One post-therapy death occurred due to gunshot wound after the participant was discontinued from the study due to noncompliance with investigational product, which was considered unrelated to the study treatment by the investigator.

Five participants experienced a total of 6 SAEs during the study; 3 of the SAEs were considered to be related to investigational product by the investigator, of which 2 SAEs (pneumonia and sepsis) reported by 1 participant in the 60 mg QD to 100 mg QW group were considered not related to investigational product by the sponsor. The participant had 1 dose of PF-06700841 60 mg on Day 1 and had 2 SAEs of pneumonia and sepsis on Day 2 before dosing and was permanently discontinued from study due to the SAE of pneumonia.

One participant in the 30 to 10 mg group was found to have a positive urine human chorionic gonadotropin test at the Week 6 (Day 42) visit after which confirmation with serum pregnancy test led to permanent discontinuation from study on Day 53. On Day 165, an obstetrical ultrasound demonstrated a right-sided cleft lip with a gap of 10 millimeters in the fetus, with no definite cleft palate. The Day 176 obstetrical ultrasound confirmed presence of cleft lip in the fetus, with all other findings appearing within normal limits. This event of fetal cleft lip was unexpected in the single reference safety document for the investigational product and was assessed as related per sponsor.

No participants experienced herpes zoster during the study. Six participants experienced AEs of herpes simplex; 5 were mild in severity and 1 was a moderate AE of herpes simplex reported by 1 participant in the 60 mg QD to 100 mg QW group during the induction period.

One participant in the 30 mg QD to 100 mg QW group was reported to have an AE of squamous cell carcinoma of the skin on Day 2. The AE was mild and not related to the investigational product as evaluated by the investigator, and resolved on Day 57.

Serious infections (pneumonia and sepsis) were reported for 1 participant in the 60 mg QD to 100 mg QW group. The participant only had 1 dose of PF-06700841 60 mg on Day 1 and the serious infections (pneumonia and sepsis) occurred on Day 2 before dosing.

There were no clinically meaningful observable dose dependent neutropenia, lymphopenia, thrombocytopenia, and anemia among the active treatment groups, except for 1 SAE of anemia reported by 1 participant in the 60 to 10 mg QD group. The same participant had pre-existing kidney dysfunction (chronic kidney disease Stage 3), and increased SCr and serum Cystatin-C values (1.3 mg/dL [reference range: 0.4 to 1.2 mg/dL], 1.72 mg/L [reference range: 0.53 to 0.95 mg/L], respectively) at screening. During the study, the participant developed a moderate AE of acute kidney dysfunction and concomitant ≥30% decreases from baseline in SCr based and serum Cystatin-C based eGFR, which were considered as individual clinically significant laboratory abnormalities.

No participants met the laboratory test discontinuation criteria (laboratory test abnormalities confirmed through re-testing within 48 hours) during study treatment. There was no potential Hy's Law case reported during the study.

There were no clinical meaningful findings in vital signs, ECG, and suicidal behavior or ideation during the study.

PF-06700841 is currently being investigated in patients with PsO (B7931023, topical), alopecia areata (B7931005), atopic dermatitis (B7931022, topical), ulcerative colitis (B7981005), psoriatic arthritis (B7931030), systemic lupus erythematosus (B7931028) and Crohn's disease (B7981007). All Phase 2b studies are ongoing and blinded.

Further details on the clinical safety information with PF-06700841 are provided in the IB.

2.2.8. Clinical Pharmacology of PF-06700841

Following single oral PF-06700841 doses, peak plasma concentrations generally occurred at or before 1 hour for doses of 1 mg-200 mg. In general, both AUC_{inf} and C_{max} appeared to increase proportionally with dose from 1 mg-100 mg; there appeared to be a trend toward more than proportional increase from 100 mg-200 mg. Mean $t_{½}$ was 3.8-7.5 hours with a trend towards longer $t_{½}$ at the higher doses, probably due to concentrations remaining above the lower limit of quantification (LLOQ) for a longer time as the dose increased.

On Day 10 of multiple-dose administration, PF-06700841 was absorbed rapidly with median T_{max} 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_{tau} both appeared to increase proportionally with dose from 10 mg QD to 100 mg QD with a trend towards greater than proportional increase from 100 mg to 175 mg QD. As would be expected, dose normalized C_{max} for 50 mg BID is slightly higher than that for 100 mg QD while dose normalized AUC_{tau} is consistent between the two dosing regimens. Mean terminal $t_{½}$ ranged from 4.9 to 10.7 hours. Steady state generally appeared to have been reached by Day 8 of QD or BID dosing. Urinary recovery of PF-06700841 was low, with less than 16% of the dose recovered unchanged.

Following multiple-dose administration in participants with PsO, PF-06700841 was absorbed rapidly with median T_{max} of 1 to 2 hours post dose. Mean terminal $t_{½}$ was 16 hours in the 30 mg group and 6 hours in the 100 mg group. The mean $t_{½}$ value in the 30 mg group included a reported $t_{½}$ 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 LLOQ after 24 hours and $t_{½}$ values of 6.48 hours or less.

Relative BA of 100 mg PF-06700841 tablets compared to 100 mg oral suspension was 96.18% for AUC_{inf} and 94.28% for C_{max}. Both of the 90% CIs for the ratio were within the 80%-125% equivalence interval. When the 100 mg tablets were administered under fed conditions, T_{max} was delayed with a median value of 4.0 hours, compared to 0.5 hours under fasted conditions. For 100 mg tablets fed versus fasted, the ratio (90% CI) of adjusted geometric means for AUC_{inf} and C_{max} was 82.33% (73.45%, 92.29%) and 64.25% (55.98%, 73.75%), respectively. The results indicate that PF-06700841 can be administered with or without food.

Following single oral dose of PF-06700841 100 mg under fasted conditions in Japanese participants (B7931009), absorption was rapid with a median T_{max} of 1 hour and a range of 0.5-2 hours on Day 1. Geometric mean AUC_{inf} was 8725 ng•hr/mL and C_{max} was 1035 ng/mL. Mean terminal $t_{½}$ was 5.7 hours based on a 24-hour sampling.

On Day 10 following multiple oral dosing, median T_{max} was 0.76 hours with a range of 0.5-4.0 hours. Both AUC_{tau} and C_{max} increased slightly compared to Day 1, with geometric mean values of 9888 ng•hr/mL and 1114 ng/mL, respectively. Mean terminal $t_{½}$ was 8.9 hours. Steady-state generally appeared to have been achieved by Day 6. Urinary recovery of PF-06700841 was low, with less than 16% of the dose recovered unchanged.

Following a single dose of 200 mg PF-06700841 in B7931019, the maximum placebo-corrected QTcF change from baseline was observed at 3 hours post-dose with mean of 14.6 ms and 90% confidence interval (CI) of (12.4, 16.8 ms). In addition, the maximum mean change in QTcF observed following administration of 400 mg moxifloxacin was 13.8 ms (90% CI: 11.6, 16.0 ms), suggesting a good sensitivity in this QT study.

Per protocol, concentration-QTcF analysis was pre-defined as the primary analysis to determine PF-06700841 effects on QT prolongation at relevant clinical doses. The results described here are considered as preliminary data as the Clinical Study Report is being drafted.

The relationship between PF-06700841 concentration and QTcF change from baseline was best and adequately described by E_{max} model, in which the maximum QTcF change (E_{max}) was estimated to be 15.7 ms (90% CI: 13.2, 18.2 ms). The QTcF change observed at 200 mg PF-06700841 appeared to reach maximum effect. Based on concentration-QT model, the estimated mean change in QTcF at steady-state C_{max} of 45 mg QD was 7.7 ms (90%CI: 6.5, 9.1 ms). This suggested that no clinically significant QT effect expected following PF-06700841 treatment up to 45 mg QD as the upper bound of two-sided 90% CI is less than 10 ms threshold. Following PF-06700841 60 mg QD, the highest clinical dose being tested in Phase 2/2b studies, the mean QTcF change at expected C_{max} were 8.8 ms (90%CI: 7.7, 10.2 ms) with the upper bound slightly exceeding 10 ms.

B7931004 study was recently completed and clinical study report is ongoing. In study B7931004, PF-06700841 plasma concentrations were collected pre-dose at each visit from the baseline visit, and for Weeks 1, 2, 4, 6, 8, 10, and 12; at ~0.5 hours post-dose for the Week 2, 4, 6, 8, 10, and 12 visits, and at 1, 2, and 4 hours (±30 min) post-dose for the Week 4 and Week 12 visits.

Plasma concentrations of PF-06700841 observed were as expected based on PK in healthy participants.

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2.2.10. Nonclinical Safety of PF-06826647

No adverse findings were observed in oral repeat dose toxicity studies with PF-06826647 in rats and monkeys up to 6 and 9 months in duration, respectively. Test article related, nonadverse, target organs identified include the immune and hemolymphatic systems (thymus, spleen, lymph nodes, bone marrow, erythron, and leukon), liver (increased transaminases), and bone (increased trabecular thickness). The findings in the immune and hemolymphatic systems are consistent with the pharmacological activity of PF-06826647. In the 6-month toxicity study in rats, the NOAEL was 500 mg/kg/day [250 mg/kg twice daily (BID)] with unbound maximum concentration C_{max} of 1680 ng/mL, and unbound AUC_{24} (area under the curve 24 hours) of 16,600 ng•h/mL. In the 9-month toxicity study in monkeys, the NOAEL was 220 mg/kg/day with unbound C_{max} of 663 ng/mL and unbound AUC_{24} of 8130 ng•h/mL, respectively.

In an EFD study in rabbits, adverse PF-06826647-related embryolethality due to higher incidence of late resorptions resulting in higher postimplantation loss and lower number of live fetuses was observed at 500 mg/kg/day (unbound C_{max} of 1290 ng/mL and AUC_{24} of 17,300 ng•h/mL). The developmental NOAEL in rats was 500 mg/kg/day (unbound C_{max} of 1850 ng/mL and AUC_{24} of 19,600 ng•h/mL), and in rabbits was 150 mg/kg/day (unbound C_{max} of 864 ng/mL and AUC_{24} of 9930 ng•h/mL).

PF-06826647 was not mutagenic in bacterial reverse mutation assays. Although PF-06826647 was positive for micronuclei formation in vitro (through an aneugenic mechanism), it did not induce micronuclei in vivo in rats at 500 mg/kg/day (250 mg/kg BID) (unbound C_{max} of 2110 ng/mL and AUC_{24} of 24,100 ng•h/mL), the highest dose tested in the 1-month study. No evidence of PF-06826647 related phototoxicity in the skin or eyes of pigmented rats in a 3-day phototoxicity study was observed up to the highest dose tested of 500 mg/kg/day (250 mg/kg/BID), demonstrating that PF-06826647 was not a phototoxicant, in vivo.

Further details of the nonclinical safety program of PF-06826647 are provided in the current IB.

2.2.11. Clinical Safety of PF-06826647

As of 19 October 2018, the clinical development program for PF-06826647 was comprised of an ongoing placebo-controlled Phase 1 study (C2501001). In this study, six SAD cohorts and five MAD cohorts in healthy participants have been completed, with 54 healthy adult participants randomized and treated with PF-06826647 or placebo; an ongoing study is evaluating a cohort of 6 healthy Japanese participants receiving 400 mg QD, along with 2 cohorts of participants with moderate to severe plaque PsO receiving 400 mg or 100 mg QD of PF-06826647 or placebo. PsO participants receiving active treatment with PF-06826647 (100 mg or 400 mg QD for 28 days) had clinically meaningful decreases in disease activity as measured by Psoriasis Area and Severity Index (PASI), the defined primary endpoint.

Preliminary safety, efficacy, and pharmacodynamic (PD) results from this study support further development of PF-06826647 in plaque PsO. The Phase 1 study (C2501001) demonstrated an acceptable safety and PK profile at single doses of PF-06826647 ranging from 3 mg to 1600 mg in the SAD portion and ten-day doses from 10 mg to 1200 mg daily in the MAD portion of the study. Dose escalation stopping rules were not triggered. There were no clinically meaningful findings in vital signs, ECGs, or potential Hy's Law cases reported during this study. In addition, there have been no serious AEs (including death) or suspected, unexpected, serious adverse reactions (SUSARs) reported. Based on preliminary review of treatment group data, all reported TEAEs have been of mild intensity.

Further details on the clinical safety information with PF-06826647 are provided in the IB.

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2.3. Benefit/Risk Assessment

Currently, adalimumab is the only approved medical treatment for moderate to severe HS. However, a significant number of patients (~40%) with moderate to severe HS, did not respond to treatment with adalimumab.

As described in Section 2 (Introduction), the pathophysiology of HS remains incompletely defined, and numerous inflammatory mediators have been implicated in the disease.

PF-06650833 is a highly selective, small molecule inhibitor of IRAK4. IRAK4 is a key node in the signal transduction of many tool-like receptors (TLR)- induced pro-inflammatory pathways.

PF-06650833 has been evaluated in multiple Phase 1 studies in healthy participants, and in a Phase 2, dose-ranging, 12-week study in participants with moderate to severe rheumatoid arthritis (RA). PF-06650833 appears to be generally safe and effective up to 400 mg administered QD for 12 weeks in participants with RA (Study B7921005, Section 2.2.3).

PF-06700841 is a dual TYK2/JAK1 inhibitor. Based on its cytokine inhibition profile, PF-06700841 is expected to target the T-helper (TH)17 pathway directly by inhibiting TYK2 and indirectly by inhibiting JAK1.

PF-06700841 has been evaluated in multiple Phase 1 studies and in participants with plaque psoriasis. PF-06700841 is currently being investigated in participants with psoriasis, alopecia areata, atopic dermatitis, ulcerative colitis, and Crohn's disease. The overall safety profile to date with PF-06700841 has been acceptable with doses up to 60 mg QD for 4 weeks and 30 mg QD for up to 20 weeks in completed studies (Section 2.2.7).

PF-06826647 is a potent TYK2 inhibitor. Based on its cytokine inhibition profile, PF-06826647 is expected to target the TH1 and TH17 pathways, and Types I and II interferon signaling, directly by inhibiting TYK2, and to provide therapeutic benefit in the treatment of inflammatory conditions driven by TH1/TH17 and interferon immune responses.

PF-06826647 has been evaluated in a Phase 1 study (C2501001) in healthy participants and in two cohorts of participants with moderate to severe plaque psoriasis. A second study in participants with moderate to severe plaque psoriasis is ongoing. PF-06826647 appears to be safe up to 1600 mg administered as a single dose, and 1200 mg as multiple doses (up to 4 weeks).

For this current study, the dose rationale for PF-06650833, PF-06700841 and PF-06826647 are detailed in Section 4.3.

Overall, the safety profile observed to date for PF-06650833, PF-06700841 and PF-06826647 appears to be acceptable at the respective oral dosages (ie, 400 mg QD, 45 mg QD and 400 mg QD) to be evaluated in this study. The potential benefits of PF-06650833, PF-06700841 and PF-06826647 is expected to outweigh the potential risks for participants with moderate to severe HS.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-06650833, PF-06700841 and PF-06826647 may be found in the respective IBs, which are the single reference safety documents (SRSD) for this study.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
To evaluate the efficacy of PF-06650833, PF-06700841, and PF-06826647 vs placebo in participants with HS as assessed by HiSCR.	Percentage of participants with HiSCR response* at Week 16.	This estimand uses a composite estimand theory (ICH E9 addendum) and is intended to provide a population level estimate of the treatment effect of the IP on a binary endpoint regardless of participant compliance with the IP dosing. Population-level summary: difference between treated and placebo in proportion of participants with HiSCR response at Week 16.
Secondary:	**Secondary:**	**Secondary:**
To evaluate the efficacy of PF-06650833, PF-06700841, and PF-06826647 vs placebo in participants with HS at Week 16 and over time.	Percentage of participants with HiSCR response* at Weeks 1, 2, 4, 6, 8, and 12. Percentage of participants with a total abscess and inflammatory nodule (AN) count of 0 or 1; 0, 1, or 2 at Week 16.	This estimand is intended to provide a population level estimate of the treatment effect of the IP on a binary endpoint regardless of participant compliance with the IP dosing. Population-level summary: difference between treated and placebo in proportion of participants with HiSCR response at Weeks 1, 2, 4, 6, 8 and 12, respectively; difference between treated and placebo in proportion of participants with a total AN count of 0 or 1, or 0, 1 or 2, respectively at Week 16.

	Percent change from baseline (CFB) in AN count at Weeks 1, 2, 4, 6, 8, 12 and 16.	This estimand is intended to provide a population level estimate of the treatment effect of the IP on a continuous endpoint regardless of participant compliance with the IP dosing. Population-level summary: difference between treated and placebo change from baseline in AN count at Weeks 1, 2, 4, 6, 8, 12 and 16.
To evaluate the efficacy of PF-06650833, PF-06700841, and PF-06826647 vs placebo on International Hidradenitis Suppurativa Severity Score System (IHS4).	Absolute score and percent CFB in IHS4 at Weeks 1, 2, 4, 6, 8, 12 and 16.	This estimand is intended to provide a population level estimate of the treatment effect of the IP on a continuous endpoint regardless of participant compliance with the IP dosing. Population-level summary: difference between treated and placebo in absolute score and change from baseline on IHS4 at Weeks 1, 2, 4, 6, 8, 12 and 16.
To evaluate the effects of PF-06650833, PF-06700841, and PF-06826647 vs placebo on HS flare.	Proportion of participants who experience an HS flare, defined as at least a 25% increase in AN count with a minimum increase of 2 relative to Baseline, at Weeks 4, 8, 12 and 16.	The estimand is intended to provide a population level estimate of the treatment effect of the IP on a binary endpoint regardless of participant compliance with IP dosing. Population-level summary: difference between treated and placebo in proportion of participants experience flare at Weeks 4, 8, 12 and 16.
To evaluate the efficacy of PF-06650833, PF-06700841, and PF-06826647 vs placebo on pain and pain reduction over time in participants with HS.	Percentage of participants with ≥30% reduction and ≥1-unit reduction from baseline in PGA-Skin Pain numeric rating scale (NRS30) – at worst and on average, respectively, amongst participants with baseline NRS ≥3, at Weeks 1, 2, 4, 6, 8, 12 and 16. Percent CFB in NRS, at worst and on average respectively, in participants who have baseline NRS ≥3, at Weeks 1, 2, 4, 6, 8, 12 and 16.	This estimand is intended to provide a population level estimate of the treatment effect of the IP on a binary endpoint regardless of participant compliance with the IP dosing. Population-level summary: difference between treated and placebo in proportion of participants with ≥30% reduction and ≥1-unit reduction from baseline in PGA-Skin Pain NRS (NRS30), at worst

		and on average, respectively, amongst participants with baseline NRS ≥3, at Weeks 1, 2, 4, 6, 8, 12 and 16.
	CFB in NRS, at worst and on average respectively, at Weeks 1, 2, 4, 6, 8, 12 and 16.	This estimand is intended to provide a population level estimate of the treatment effect of the IP on a continuous endpoint regardless of participant compliance with the IP dosing. Population-level summary: difference between treated and placebo percent change from baseline in NRS, at worst and on average respectively, in participants who have baseline NRS ≥3, at Weeks 1, 2, 4, 6, 8, 12 and 16. Difference between treated and placebo change from baseline in NRS, at worst and on average respectively, at Weeks 1, 2, 4, 6, 8, 12 and 16.
To evaluate the efficacy of PF-06650833, PF-06700841, and PF-06826647 vs placebo on erythema.	Proportion of participants achieving erythema score of 1 or 0 in all affected anatomic regions among participants who have an erythema score of 2 or more in at least 1 anatomic region at baseline.	The estimand is intended to provide a population level estimate of the treatment effect of the IP on a binary endpoint regardless of participant compliance with IP dosing. Population-level summary: difference between treated and placebo in proportion of participants achieving erythema score of 1 or 0 in all affected anatomic regions among participants who have erythema score of 2 or more in at least 1 anatomic region at baseline.

To assess the safety and tolerability of PF-06650833, PF-06700841, and PF-06826647 vs placebo in participants with HS.	Incidence of TEAEs (AEs and SAEs), significant changes in vital signs, clinical laboratory abnormalities, and ECG.	There is no defined estimand for these endpoints and they will be analyzed using Pfizer data standards as applicable.
To evaluate the effects of PF-06650833, PF-06700841, and PF-06826647 vs placebo on patient centered outcomes in participants with HS.	Absolute score and CFB at time points specified in the SoA in HS Symptom Items and Dermatology Life Quality Index (DLQI) total score. Proportion of participants achieving a DLQI=0 or 1.	These endpoints will be analyzed descriptively and with respect to an estimand.
To evaluate the PK of PF-06650833, PF-06700841, and PF-06826647 vs placebo in participants with HS.	Summary of plasma concentration of PF-06700841, PF-06826647 and PF-06650833.	There is no defined estimand for these endpoints and they will be analyzed using Pfizer data standards as applicable.
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*HiSCR requires:

- At least a 50% reduction in the total AN count relative to baseline; and
- No increase in abscess count; and
- No increase in draining fistula count.

For all endpoints, baseline is defined as the result closest prior to dosing on Day 1.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2a, randomized, double-blind, placebo-controlled, parallel group, multicenter platform study with 3 kinase inhibitors (PF-06650833, PF-06700841 and PF-06826647) in participants with moderate to severe HS. The study will have a maximum duration of approximately 26 weeks. This includes an up-to-6-week Screening Period, a 16-week Dosing Period and a 4-week Follow-up Period. The study will enroll a total of approximately 192 participants (expected to provide approximately 156 completers). The study will be conducted globally at approximately 60 study sites. The study will not be blinded across the PF-06650833, PF-06700841 and PF-06826647 treatment arms, but will be placebo-controlled double-blinded within each IP treatment arm.

Following the screening period, participants who meet eligibility criteria at the baseline visit, will be randomly assigned to receive PF-06650833 or matching placebo in a 3:1 ratio, or PF-06700841 or matching placebo in a 3:1 ratio, or PF-06826647 or matching placebo in a 3:1 ratio. One oral dose level of each PF-06650833 (400 mg QD), PF-06700841 (45 mg QD) and PF-06826647 (400 mg QD) or matching placebo will be investigated. For analysis, placebo groups will be combined to yield final IP:placebo ratio of 1:1:1:1 for each IP and placebo. No more than 30% of enrolled participants will be inadequate anti-TNF responders. Participants will be stratified according to whether they are an inadequate anti-TNF responder or not. Additionally, no more than 20% of enrolled participants may enter the study on a background of concomitant oral antibiotic therapy for treatment of HS; the dosing regimen (dose and frequency) must have been stable for at least 8 weeks (56 days) prior to the baseline (Day 1) visit and must remain stable throughout study participation. Antibiotics taken on an "as needed" (PRN) basis are not considered a stable dose. Participants will be stratified according to whether they are on a background of concomitant antibiotic therapy or not. Further details are described in Section 6.5.1.2.

Biopsies of unaffected areas and lesional area biopsies will be collected according to the SoA at selected sites; it is expected that approximately 60 participants across these selected sites will have biopsies collected. Further details are described in Section 8.8.3 and the lab manual.

4.2. Scientific Rationale for Study Design

This study is being conducted to provide data on efficacy, safety, tolerability and PK of PF-06650833, PF-06700841 and PF-06826647 in the oral treatment of moderate to severe HS. The chronic toxicology package for each asset supports the planned study treatment duration of 16 weeks.

The treatment duration of 16 weeks in this study should allow adequate assessment of the primary endpoint of HiSCR in patients with moderate to severe HS. Prior placebo-controlled study with adalimumab on background treatment with antibiotics (PIONEER II) in patients with moderate to severe HS showed HiSCR response rate at Week 12 of 58.9% as compared to a placebo response rate of 27.6% (P<0.001).[3] The additional 4 weeks treatment period should provide a more robust efficacy and safety data for the current study, and enable a clear decision of selecting the IP for further clinical development.

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

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

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4.3. Justification for Dose

4.3.1. PF-06650833

PF-06650833 was tested as an orally administered extemporaneously prepared IR formulation in doses up to 1000 mg QID for up to 14 days in healthy participants without a dose-limiting adverse effect being demonstrated.

Therefore, based on accumulated available clinical and comprehensive nonclinical toxicity data package for PF-06650833, a 400 mg MR QD dose is expected to be safe and well-tolerated while providing the best opportunity to maximize efficacy.

4.3.2. PF-06700841

In this Phase 2a study, a single dose of 45 mg of PF-06700841 will be administered once a day (QD) for 16 weeks in comparison to placebo. This dose was selected based on the safety and efficacy observed to date with PF-06700841 in healthy participants (B7931001) and

participants with active PsO (B7931001 and B7931004) and AA with more than 50% hair loss (B7931005). The overall safety profile to date with PF-06700841 has been acceptable with doses up to 60 mg QD for 4 weeks and 30 mg QD for up to 20 weeks in completed studies. Ongoing studies in inflammatory bowel disease (IBD) are assessing the 60 mg QD dose for up to 12 weeks, and an extended period at 30 mg QD for up to 52 weeks.

Based on the preliminary population PK analysis with combined data from studies B7931001 in healthy participants and B7931004 in patients with moderate to severe PsO, the expected median steady state exposures (AUC_{24}) following 45 mg QD is 2030 ng.h/mL, in a patient population. As a result, the exposure of PF-06700841 (AUC_{24}) at 45 mg QD in this study are expected to be 56x and 8.6x below the AUC_{24} at the NOAELs observed in the 6-month rat (45 mg/kg/day) and 9-month monkey (20 mg/kg/day) studies, respectively. The pharmacological activity of PF-06700841 was assessed by reduction of hsCRP in patients with moderate to severe PsO (B7931004). In study B7931004, the median reduction (percent change from baseline) of hsCRP observed at Week 4 were approximately 61% and 76% with PF-06700841 30 and 60 mg QD treatment, respectively. Study B7931004 also showed that PF-06700841 reached maximal effect on hsCRP within approximately 2 weeks after start of treatment and remained constant throughout the 12-week treatment period. The median hsCRP reduction with PF-06700841 45 mg daily dose up to 16 weeks would expect to be between 61% to 76% in patients with HS.

4.3.3. PF-06826647

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

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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 follow-up visit, shown in the SoA.

The end of the study is defined as the date of the last visit by the last participant in the study across all sites 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 Visit 1 (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 (or recognizable symptoms consistent with a diagnosis) of moderate to severe HS for at least one year (365 days) prior to Visit 1 (screening).

3. HS lesions (Hurley Stage II-III) present in at least two distinct anatomic areas (eg, left and right axilla; or left axilla and left inguino-crural fold).

4. Inadequate response to at least a 4-week (28 day) treatment with an oral antibiotic for the treatment of HS, or for whom oral antibiotic treatments are otherwise medically inadvisable (eg, because of important side effects or safety risks).

    Note: Enrollment of participants on a background of concomitant oral antibiotic therapy for treatment of HS will be limited to ≤20% of total participant population. The dosing regimen (dose and frequency) of concomitant oral antibiotic therapy must have been stable for at least 8 weeks (56 days) prior to the baseline (Day 1) visit and must remain stable throughout study participation.

5. Anti-TNF naïve; or

    Has initiated **only** one anti-TNF treatment including participants with inadequate response to the anti-TNF;

    Note: participants who initiated more than one anti-TNF treatments are not eligible.

    Enrollment of participants with inadequate response to **one** anti-TNF will be limited to ≤30% of total participant population.

    Inadequate response to **one** TNF-inhibiting biologic agent administered in accordance with its labeling recommendations. The TNF-inhibiting biologic could have been discontinued due to its being deemed inadequately effective and/or not tolerated as defined, for the purpose of this study, by the Investigator's and participant's opinions that the participant did not experience adequate benefit from the anti-TNF plus the presence of sufficient residual disease activity to meet the entry criteria. The anti-TNF biologic could also have been discontinued due to lack of continued access. The anti-TNF s should have been discontinued for a minimum of the washout period defined as follows (biosimilars of the below agents should be considered the same as the originators):

- adalimumab (Humira®): 6 weeks.
- infliximab (Remicade®), golimumab (Simponi®): 10 weeks.
- certolizumab pegol (Cimzia®): 12 weeks.

6. Participant must agree to daily use (and through follow-up) to one of the non-prescription topical antiseptics on their HS lesions such as: chlorhexidine gluconate, benzoyl peroxide, pyrithione zinc, or dilute bleach in bathwater.

7. Total AN of ≥4 at baseline; and a draining fistula count of ≤20 at baseline.

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

Body Mass Index and Weight:

9. Body Mass Index (BMI) ≥17.5 kg/m^2 and body weight ≥40 kg.

Informed Consent:

10. 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. Evidence of other active skin disease or condition (eg, bacterial, fungal, or viral infection) at the time of screening or baseline visit that would interfere with the evaluation of HS.

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

   - 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) (See Section 8.2.7).
   - 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.
   - In the opinion of the investigator or Sponsor (or designee) exclusion is required.

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

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

5. Have acute coronary syndrome (eg, myocardial infarction, unstable angina pectoris) or any history of significant cerebrovascular disease within 24 weeks of screening.

6. 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.

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

8. History (single episode) of multidermatomal herpes zoster or disseminated herpes simplex, or a recurrent (more than one episode of) localized, 1-2 dermatomal herpes zoster.

9. History of infection (not including infection symptoms resulting from HS) requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator within 3 months (90 days) prior to first dose of IP or a history of infection requiring oral antimicrobial therapy within 2 weeks prior to the first dose of IP.

10. Infected with Mycobacterium tuberculosis (TB) (See Section 8.2.1.1).

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

12. Have any malignancies or 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.

13. Have undergone significant trauma or major surgery within 1 month (30 days) prior to screening or plan to undergo surgery during the treatment period.

14. 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 administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

Prior/Concomitant Therapy:

Refer to Section 6.5 and Appendix 9 for details regarding prohibited prior/concomitant medications.

15. Participant requires, or is expected to require, opioid analgesics for any reason.

16. Participant received prescription topical therapies for the treatment of HS within 14 days prior to the baseline (Day 1) visit.

17. Receipt of systemic therapies for HS including non-biologics with potential therapeutic impact for HS less than 28 days or within 5 half-lives (if known), whichever is longer, prior to the baseline (Day 1) visit (other than permitted antibiotics).

Prior/Concurrent Clinical Study Experience:

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

Diagnostic Assessments:

19. Screening 12-lead 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. Specifically, participants with screening Fredericia corrected QT interval (QTcF) >450 milliseconds (msec) should be excluded.

    If QTcF exceeds 450 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF should be used to determine the participant's eligibility.

20. 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).

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

    - Participants who are hepatitis C virus (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 is negative.

- Participants who are hepatitis B surface antigen (HBsAg) positive are not eligible for the study.

- Participants who are HBsAg negative and hepatitis B core antibody (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.

22. 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 <9.0 g/dL or hematocrit <30% (<0.30 v/v).

    - Absolute lymphocyte count (ALC) <1.0 x 10^9/L (<1000/mm^3).

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

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

    - eGFR <60 mL/min/1.73 m^2 using SCr or cystatin C based calculation (See Section 8.2.5.1).

    - AST or ALT ≥1.5 times the upper limit of normal (ULN).

    - Total bilirubin ≥1.5 time the ULN (for participants with a history of Gilbert's syndrome: direct bilirubin > ULN).

    - Creatinine kinase (CK) >3 times the ULN and positive urine myoglobin.

    - Positive urine drug screen.

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

Other Exclusions:

23. History of alcohol or substance abuse, unless in full remission for greater than 6 months prior to Day 1.

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

25. In the opinion of the investigator or sponsor, the participant is inappropriate for study entry.

26. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or Pfizer employees, including their family members, directly involved in the conduct of the 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 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. 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 during this same period. This is due to the potential for virus to be shed in bodily fluids (including stool) following vaccination with live component vaccines, leading to a potential risk that the virus may be transmitted.

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

5.3.3. 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 Sponsor. 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, pomelos within 7 days prior to Day 1 and until collection of the final PK blood sample.

5.3.4. Antiseptic Therapy

Participants are required to use an over-the-counter daily antiseptic wash on their HS lesions such as chlorhexidine gluconate, benzoyl peroxide, pyrithione zinc, or dilute bleach in bathwater.

5.3.5. Other Lifestyle Requirements

Participants are required to comply with fasting requirements (water only) for at least 8 hours prior to the study visits where fasting laboratory assessments are performed as indicated in the SoA. Participants should abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, and aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace is permitted. Use of nicotine containing products or ingestion of caffeine (eg, tea, coffee, some soft drinks/colas/energy drinks and power bars) is prohibited during the 30 minutes prior to BP and pulse (heart) rate measurements.

On study visit days, participants should be instructed to refrain from taking their dose of IP at home. Dosing of IP will be administered while at the study site. Prescribed permitted concomitant medication may be administered, as needed, prior to the study visit, if it can be administered with water only. Prescribed permitted concomitant medications that must be taken with food or after meals should not be taken until after the visit procedures have been completed. Participants should be instructed to contact the study site if there are any changes or additions to concomitant medications.

Participants may shower or bath prior to attending study visits; however moisturizing should be avoided.

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 IP. 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 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-screened participants will be re-consented. All screening assessments must be repeated during re-screening, with the exception of chest radiograph, HIV, Hepatitis and TB testing, provided re-screening is done within 3 months of screening. Rescreened participants should be assigned a new participant number.

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 IP may be used synonymously with study intervention.

6.1. Study Intervention(s) Administered

Intervention Name	PF-06650833	PF-06700841	PF-06826647
ARM Name	PF-06650833 400 mg Active and Placebo	PF-06700841 45 mg Active and Placebo	PF-06826647 400 mg Active and Placebo
Type	Drug	Drug	Drug
Dose Formulation	Tablet	Tablet	Tablet
Unit Dose Strength(s)	200 mg Active Placebo	25 mg, 5 mg Active Placebo	100 mg Active Placebo
Dosage Level(s)	400 mg QD	45 mg QD	400 mg QD
Route of Administration	Oral	Oral	Oral
Investigational Medicinal Product (IMP) and Noninvestigational Medicinal Product (NIMP)	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor. Refer to IP Manual.	Provided centrally by the sponsor. Refer to IP Manual.	Provided centrally by the sponsor. Refer to IP Manual.
Packaging and Labeling	CCI [redacted] IP will be blinded within the intervention only; ie, blinded to active or placebo only. Blinding will not occur across the asset line.	CCI [redacted] IP will be blinded within the intervention only; ie, blinded to active or placebo only. Blinding will not occur across the asset line.	CCI [redacted] IP will be blinded within the intervention only; ie, blinded to active or placebo only. Blinding will not occur across the asset line.
Current/Former Name(s) or Alias(es)	IRAK4	TYK2/JAK1	TYK2

6.1.1. Administration

Participants will be provided dosing instructions.

Sites will be trained on how participants should take tablets at home through an investigational product (IP) manual and/or other vehicle(s). Sites are responsible for

communicating this information to participants; and site staff should review the dosing instructions with participants at every study visit.

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

Participants will swallow the IP whole with ambient temperature water to a total volume of approximately 240 mL, and will not manipulate or chew the medication prior to swallowing. It is recommended that PF-06650833/matching placebo and PF-06700841/matching placebo be taken while fasting; PF-06826647/matching placebo must be taken with food. On IP dispensing study visit days, participants are to be instructed to refrain from dosing at home, and are to take the dose in the clinic from their current blister card/wallet or bottle.

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

6.2. Preparation/Handling/Storage/Accountability

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

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

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All study interventions will be accounted for using an IP accountability form/record. The participant will be asked to bring all dispensed IP [redacted] to the clinic at every visit. Detailed drug accountability records will be maintained by study staff for each participant.

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

The IP will be dispensed using an IRT drug management system at each IP dispensing visit per the SoA. A qualified staff member will dispense the IP CCI [redacted] provided, in quantities appropriate for the study visit schedule. The participant/caregiver should be instructed to maintain the product CCI [redacted] provided throughout the course of dosing and return CCI [redacted] to the site at the next IP dispensing study visit.

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 6.3.2 for further details.

One oral dose level of each PF-06650833 (400 mg QD), PF-06700841 (45 mg QD) and PF-06826647 (400 mg QD) plus matching placebo in a 3:1 ratio will be investigated. For analysis, placebo groups will be combined to yield final IP:placebo ratio of 1:1:1:1 for each IP and placebo.

6.3.1. Allocation to Investigational Product

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

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

Returned IP must not be redispensed to the participants.

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

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded IP records at the site(s) to verify that randomization/dispensing has been done accurately.

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 prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. 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 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.

6.4. Study Intervention Compliance

The participant will take the IP at home (except on study visits); compliance will be captured at each study visit by tablet count.

Participant compliance with IP will be assessed at each visit. At non-dispensing visits, sites should assess the CCI [redacted] for compliance however the CCI [redacted] should remain in the possession of the participant. Participants will be instructed to bring all dispensed IP supplies in the original packaging (used as well as unused) to every study visit.

Non-compliance is defined as less than 80% or more than 120% of IP dosing as directed by the dosing instructions. The investigator and the sponsor have the discretion to withdraw any participant from the study for reasons of non-compliance with the dosing regimen. Investigators should indicate on the appropriate CRF page noncompliance with study intervention and provide an explanation. Inventory control of all 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 the sponsor.

6.5. Concomitant Therapy

Medications that are taken in the Screening period (after informed consent is obtained and before the first dose of IP) 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, route of administration 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 study visit. Any new concomitant medications or dose changes to current concomitant medications should be evaluated for potential new or worsening AEs.

The start date, stop date, route of administration and indication for all therapies will be recorded on the CRF.

6.5.1. Permitted Concomitant Medications

A participant who is receiving a permitted concomitant medication for any reason must be on a locally-approved medication and dose for the treated indication, and this must be documented in the CRF. Participants are not allowed any other investigational drugs or treatments during the study.

Participants should **refrain from starting new or changing doses** of permitted prescription or non-prescription drugs, vitamins, and dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to Day 1 and prior to study visits throughout the study, unless otherwise noted below.

Participants should report any changes to permitted medications during the study to the study site as soon as they occur. Medication changes must be documented in the participant's record and CRF.

Participants may be administered medications necessary for the treatment of concomitant medical disorders as deemed necessary by the treating physician. Following Day 1, addition

of concomitant medications or any change in the dosage should be limited to those considered medically essential.

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

A participant who is receiving **metformin** as concomitant medication must allow at least two hours to elapse after taking the metformin before taking the IP.

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are women of childbearing potential (WOCBP) (see Appendix 4).

6.5.1.1. Wound Care

Concomitant use of wound care dressings on HS wounds is permitted; however, options are limited to alginates, cydrocolloids, and hydrogels.

6.5.1.2. Antibiotic Therapy

Participants may enter the study on a background of permitted concomitant oral antibiotic therapy for treatment of HS provided the dosing regimen (dose and frequency) has been stable for at least 8 weeks (56 days) prior to the baseline (Day 1) visit. The dosing regimen must remain stable throughout study participation. Antibiotics taken on a PRN basis are not considered a stable dose.

Permitted oral concomitant antibiotics include:

- Doxycycline (at a dose of up to 100 mg po BID);
- Minocycline (at a dose of up to 100 mg po BID).

If another baseline oral concomitant antibiotic for HS is medically necessitated, the Sponsor's Medical Monitor must be contacted for approval. Participants should not initiate/change background antibiotic therapy once entered into the study.

6.5.1.3. Analgesic Therapy

If a participant is on a stable dose of non-opioid analgesic, the participant may continue the analgesic, provided the dose is stable for 14 days prior to the baseline (Day 1) visit and is anticipated to remain stable throughout study participation.

If a participant's pain worsens after baseline, they may initiate analgesic therapy at any time as follows:

Permitted analgesics are limited to:

- Nonsteroidal anti-inflammatory drugs (NSAIDs) (at a dose of up to 3200 mg/day).
- Acetaminophen (at a dose of up 4 g/day).

Dose adjustments of NSAIDs or acetaminophen, and use of these analgesics on an PRN basis up to the maximum permitted dose and frequency are allowed.

Note: Analgesics should not be administered within 4 to 6 hours prior to study assessments.

Opioid analgesics (including tramadol and any products that may contain tramadol, eg, cough suppressants) are prohibited.

6.5.2. Prohibited Medications and Treatments

Participants will abstain from all concomitant medications as described in Section 5.2 and Appendix 9.

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

Please see Section 5.3.2 and Section 5.3.3 for restrictions regarding vaccinations and herbal supplements.

6.5.3. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-06650833, PF-06700841 and PF-06826647; standard medical supportive care must be provided to manage the AEs.

Participants requiring rescue medication will be discontinued from IP dosing and will enter the Follow-up Period.

6.6. Dose Modification

No dose adjustment is allowed during the study.

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

For participants who discontinue early, the Early Termination (ET) visit assessments will be performed. 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 AEs have resolved, returned to a baseline state, or are deemed clinically stable.

For Guidelines for Monitoring and Discontinuations refer to Appendix 8.

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 per SoA. The site will inform the Sponsor if the criteria for permanent discontinuation of the IP defined in Appendix 8 are triggered.

Any participant meeting discontinuation criteria must have the procedures scheduled for ET Visit performed on the last day the subject takes the investigational product or as soon as possible thereafter and enter into Follow-up with their end of study (EOS) visit occurring approximately 4 weeks after their ET Visit.

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

7.2. Participant Discontinuation/Withdrawal From the Study

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

At the time of discontinuing from the study, if possible, an early 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 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 remain in the study and must continue to be followed for protocol-specified follow-up procedures. 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 IP 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. All screening labs are assessed by the study-specific laboratory and confirmed by a single repeat, if deemed necessary. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

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

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

The total blood sampling volume for individual participants in this study does not exceed 550 mL during any period of 60 consecutive days. 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

8.1.1. Hidradenitis Suppurativa Clinical Response (HiSCR)

Hidradenitis suppurativa clinical response, the primary endpoint used, is defined as:

- At least a 50% reduction in the total AN count relative to baseline, **and**
- No increase in abscess count, **and**
- No increase in draining fistula count

8.1.1.1. Lesion Counts

The number of inflammatory and non-inflammatory nodules, abscesses, draining and non-draining fistulas, and hypertrophic scars, as well as the physical location (right/left axilla, right/left inframammary, intermammary, right/left buttock, right/left inguino-crural fold, perianal, perineal, other) will be assessed according to the SoA.

8.1.1.1.1. Abscess Count

Number of abscesses (fluctuant, with or without drainage, tender or painful) will be counted in each of the regions as defined above.

8.1.1.1.2. Inflammatory Nodule Count

Number of inflammatory nodules (tender, erythematous, pyogenic granuloma lesion) will be counted in each of the regions as defined above.

8.1.1.1.3. Fistula Count

Number of fistula (sinus tracts, with communications to skin surface, draining purulent fluid) will be counted in each of the regions as defined above.

8.1.2. Hurley Staging

Hurley staging is defined as follows:

- Stage I: Abscess formation, single or multiple, without sinus tracts and cicatrization (scarring).
- Stage II: One or more widely separated recurrent abscesses with tract formation and cicatrization (scars).
- Stage III: Multiple interconnected tracts and abscesses across the entire area, with diffuse or near diffuse involvement.

Hurley staging will be performed according to the SoA.

CCI [redacted]

CCI [redacted]

8.1.4. Erythema Assessment

The overall degree of erythema will be assessed for each anatomic region affected by HS using a four-point ordinal scale ranging between 0 (no redness), 1 (faint but discernible pink coloration), 2 (moderate red coloration), or 3 (very red or bright red coloration).

8.1.5. International Hidradenitis Suppurativa Severity Score System (IHS4 Score)

The IHS4 score is calculated by the number of nodules, the number of abscesses, and the number of draining tunnels. IHS4 score will be calculated according to the SoA.

IHS4 score = (number of nodules × 1) + (number of abscesses × 2) + {number of draining tunnels (fistulae/sinuses) × 4}.[20]

8.1.6. 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. Every effort should be made to ensure consistency in evaluations; therefore, the same rater should evaluate the same study participants throughout the trial.

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 TB either using Interferon Gamma Release Assay (IGRA) test or Mantoux/Purified Protein Derivative (PPD) tuberculin skin test. This will be performed at 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 test (QFT-G), QuantiFERON®-TB Gold Plus (QFT-plus) 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-plus 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

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

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

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

8.2.1.3. Medical History

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

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.

8.2.2. Physical Examinations (Full Physical and Brief Physical)

Full physical examinations must be performed by 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, GI, and

neurological systems. Investigators should pay special attention to clinical signs related to previous serious illnesses.

A brief physical examination will include assessments of the skin, heart, lung, abdomen, 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 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 the SoA.

8.2.2.1. HS Lesion Photography (at selected sites only)

HS lesion photography is optional, may be available only at selected study sites and will be performed at time points specified in the SoA. HS lesion photography will be a photographic documentation of representative lesion(s) and will be performed using a digital camera approved by the Sponsor or delegate. Both an overview and regional lesion photo may be taken. The procedure will be described in a separate manual that will be provided prior to first participant first dose. All images acquired must be saved by the site until the conclusion of the study.

Photographic images are primarily taken for documentation and publication. They may be reviewed and evaluated by a central review facility and/or the Sponsor. This central image review will not be a medical review of the study participant and no incidental findings will be shared with the investigator, other site staff, or the study participant. Review of these skin areas captured in the photographic images for any potential safety or tolerability concerns will be done by the site staff during the visit.

8.2.2.2. Height and Weight

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.

8.2.3. Vital Signs

Temperature (Oral, Tympanic, Axillary or Temporal), pulse rate and BP will be assessed. It is preferred that body temperature be collected using the same method for the same participant throughout the study. Axillary temperature assessments should be avoided in cases where the axillary region is affected by HS.

BP and pulse rate measurements will be assessed with a completely automated device in a supine position. 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. BP and pulse rate measurements should be preceded by at least 5 minutes of rest.

8.2.4. Electrocardiograms

Standard 12-Lead ECGs should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position and prior to any blood collections (except for the post dose ECG). ECGs will be read and interpreted centrally, however to ensure safety of the participants, a qualified individual (investigator or sub-investigator) at the investigative site will perform the initial ECG read and make comparisons to baseline measurements.

On Day 1 Visit, triplicate ECGs will be obtained, and the average of the triplicate ECG measurements will serve as the participant's baseline value. If the Day 1 ECG is missing, then the screening ECG will serve as baseline value. On Weeks 8 and 16 single ECGs will be collected prior to dosing and also at 2 hours (with a ±15 minutes window) post dose.

A paper or digital copy of the ECG should be filed in the participant's chart and must be available to the sponsor upon request. Any clinically significant changes will be recorded as AEs and evaluated further, as clinically warranted. In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality.

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). Participants with QTc prolongation ≥30 msec from the baseline and >450 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG for greater than 4 hours should discontinue treatment as described in Appendix 8.

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.

8.2.5. 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.

8.2.5.1. Creatinine, Cystatin C, and Estimates of Glomerular Filtration Rate

Serum creatinine (Scr) is the best known standard test for monitoring renal function. However, SCr based 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 SCr. The most reliable estimates of glomerular filtration rate (GFR) use both test results.[8]

Serum cystatin C is a low molecular weight protein that is used as an alternative to SCr for monitoring of renal function. It seems to correlate more closely with GFR than SCr concentration and may be a more sensitive detector of early renal dysfunction.[9,10] While use of cystatin C has been limited, its independence of demographic factors (eg, race) has made it an interesting means of determining changes in renal function in clinical settings and it is included in the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. Estimated GFR may be calculated via the 2012 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine, cystatin C, or creatinine-Cystatin C equations.[11]

Serum creatinine will be measured as part of serum chemistry at times specified in the SoA 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 SoA.

In this study, the eGFR will be calculated using the 2 sets of equations developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI),[12] which utilize SCr and serum Cystatin C (S Cystatin C) respectively[12] (See Appendix 10).

8.2.6. Herpetiform Rash Surveillance

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

8.2.7. Suicidal Ideation and Behavior Risk Monitoring

Participants meeting exclusionary criteria (See 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.

8.2.7.1. Columbia Suicide Severity Rating Scale

The C-SSRS is a validated tool to evaluate suicidal ideation and behavior[13] (See Appendix 11). It is administered by the investigator or site staff who have been trained to administer the scale. "Lifetime" version will be used at screening. "Post-baseline" version will be used at Week 8 and 16 visits.

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

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

8.2.8. 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 IP. 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 (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 IP), through and including a minimum of 28 calendar days after the last administration of the IP.

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 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 IP 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 IP 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 IP by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the IP 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 IP;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

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

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

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

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

8.4. Treatment of Overdose

For this study, any dose of PF-06650833, PF-06700841 or PF-06826647 greater than the randomized daily dose 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 the assigned IP can no longer be detected systemically (at least 3 days).

3. Obtain a blood sample for PK analysis within 3 days 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.

8.5. Pharmacokinetics

8.5.1. Plasma for Analysis of PF-06650833, PF-06700841 and PF-06826647

During all study periods, blood samples will be collected into appropriately labeled tubes containing K_2EDTA at times specified in the SoA section of the protocol for measurement of PF-06650833 and metabolites, PF-06700841 and PF-06826647.

Blood will be collected at the time points identified in the SoA section of the protocol. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. The date and exact time of the sample collection is to be noted on the source document and data collection tool (eg, CRF). Samples obtained outside the windows specified in the SoA will be considered a protocol deviation.

- Further details regarding the collection, processing, storage and shipping of the blood samples will be provided in the lab manual.

- Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

[redacted]

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Drug concentration information that may unblind the study will not be reported to investigator sites or blinded personnel.

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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: patient's global assessment (PGA) of Skin Pain NRS and HS Symptoms will be completed as a daily diary from baseline Day -7 through Week 16 at home. At Follow-up (FU) visit and ET visit (if applicable), PGA of Skin Pain NRS and HS Symptoms will be completed at site. At site visits, participants will complete PROs in the following order: Dermatology Life Quality Index (DLQI), CCI [redacted]. The amount of time required for a participant to complete the PRO questionnaires is approximately 15 minutes (depending on the visit and associated PROs).

Once participants meet all eligibility criteria, they will be provided a handheld device (provided by the sponsor) for the PGA Skin Pain NRS and HS Symptom Items. All other PROs will be completed on site prior to other study procedures. All PROs are to be completed as per the time points defined in the SoA.

Delegated site staff will oversee the use of electronic Patient Reported Outcomes (ePRO) devices. At screening, sites should emphasize the importance of completing the diary every day and ensure that the patient does not have any questions about the device or assessment completion schedule. 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. Less than 80% ePRO compliance will be reported as protocol deviation.

8.10.1. HS Symptom Items

The HS symptoms items are 5 single items that will assess patient self-reported symptoms related to HS. The participants are asked to rate each symptom on a 0 to 10 numerical rating scale, with 0 indicating no symptom experience and 10 indicating the worst possible symptom. The symptoms assessed include: pain, tenderness, swelling, tiredness, and bother of lesion appearance.

Participants should complete the HS Symptoms Items according to the SoA.

8.10.2. PGA Skin Pain Numeric Rating Scale (NRS) Items

The PGA of Skin Pain NRS will be used to assess the worst skin pain and the average skin pain due to HS. Ratings for the 2 items range from 0 (no skin pain) to 10 (skin pain as bad as you can imagine). The assessments will be completed on a daily diary by participants before they went to bed (except for FU Visit and ET visit) and responded to the items based on a

recall period of the "last 24 hours." The PGA of Skin Pain NRS will also be completed at site at FU visit and ET visit (if applicable).

Participants should complete the PGA Skin Pain NRS Items according to the SoA. The last 7 assessments prior to the date of first dose of investigational product will be averaged and serve as the participant's baseline.

8.10.3. Dermatology Life Quality Index (DLQI)

The DLQI is a general dermatology questionnaire that consists of 10 items that assess patient health-related quality of life (daily activities, personal relationships, symptoms and feelings, leisure, work and school, and treatment) over the last week.[14] The DLQI is a psychometrically valid and reliable instrument that has been translated into several languages, and the DLQI total scores and been shown to be responsive to change.

Participants should complete the DLQI according to the SoA.

CCI [redacted]

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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 treatment effect on proportion of participants with HiSCR response at Week 16 for the active treatment group relative to placebo without regard to IP compliance.

Hidradenitis suppurativa clinical response, the primary endpoint used, is defined as:

- At least a 50% reduction in the total AN count relative to baseline; **and**
- No increase in abscess count; **and**
- No increase in draining fistula count.

The population-based treatment effect will be the differences in the proportion of participants with HiSCR response at Week 16 in each active treatment arm compared to the combined placebo group.

The binary secondary estimand will be the population treatment effect on the proportion of participants with a total abscess and AN count of 0 or 1 at Week 16, for active treatment group relative to placebo group without regard to compliance with IP. The population-based treatment effect will be the differences in the proportions of success in each treatment arm compared to the combined placebo.

The continuous secondary estimand will be the population treatment effect on the continuous endpoint for NRS. The population level summary is the difference between treated and placebo in percent change from baseline in NRS at worst in participants who have baseline NRS ≥3, at Week 16. Intercurrent event for the continuous secondary estimand: withdrawal and all other events leading to missing data will be imputed in the active treatment arms using a jump to control method using the distribution of the placebo group (ie, missing data

in active treatment participants will be imputed from the distribution of matching placebo participants). Inadequate compliance participants data will be used as is.

All other secondary binary clinical endpoints, using various definitions and at different time points, will be analyzed using the primary estimand and binary secondary estimand, while all other secondary continuous clinical endpoints, using various definitions and at different time points, will be analyzed by comparing the scores of the active treatment group with the placebo group, as in the continuous secondary estimand. CCI [redacted] Details of these analyses will be presented in the SAP.

9.2. Sample Size Determination

Sample size calculation is based on the primary endpoint of HiSCR response at 16 weeks. A total of approximately 192 participants will be randomized in 3 active treatment groups (48/arm) and their matching placebo groups (16/arm) to have 39 completers for each active treatment arm, assuming a 15% dropout rate and the active treatment arm HiSCR response rate of 60% and placebo HiSCR rate of 30% (approximated based on the PIONEER 1 and II studies).[3] Statistical comparisons will be made between each of the active treatment arms against the 3 placebo groups pooled together. With one-sided family-wise error rate of 0.1 with a Bonferroni correction (0.033 after Bonferroni adjustment for 3 comparisons), this sample size will provide approximately 80% power. No statistical comparisons will be done between active treatment arms.

9.3. Populations for Analysis

For purposes of analysis, the following populations are defined:

Population	Description
Full Analysis Set (FAS)	All participants randomized and receiving at least one dose of IP.
Per-protocol analysis set (PPAS)	All participants randomized and receiving at least one dose of IP, with both baseline and Week 16 primary efficacy data, and without protocol deviations that were thought to impact the efficacy evaluation during the treatment period. All protocol deviations will be reviewed and assessed by the study team prior to database release.
Safety	All participants randomly assigned to IP and who take at least 1 dose of IP. Participants will be analyzed according to the product they actually received.

Defined Population for Analysis	Description
PK concentration set	All enrolled participants who take at least one dose of active PF-06700841, PF-06826647 or PF-06650833 and in whom at least one concentration value is reported.
PD Analysis set	All enrolled participants who take at least one dose of PF-06700841, PF-06826647 or PF-06650833 and in whom at least one value of PD parameter of interest is reported.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data, and any sensitivity analyses, subgroup analyses. 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	• The primary efficacy endpoint is the HiSCR response at Week 16. The HiSCR response data comparing active treatment group and placebo group will be analyzed using the Cochran Mantel Hanzel (CMH) test, adjusting for the stratification factor of prior anti-TNF failure status and concomitant use of antibiotics status. Treatment differences in HiSCR response and the corresponding 2-sided 80% confidence intervals adjusting for the stratification factor will be computed using the methods proposed by Cochran with the minimum risk weights proposed by Mehrotra and Railkar. More details and sensitivity analyses will be documented in the SAP. The population for the primary analysis will be based on the FAS. Sensitivity analysis will be performed using the PPAS. All missing values will be imputed as non-response to treatment.
Secondary	• The binary secondary efficacy endpoint of proportion of participants with a total AN count of 0 or 1 at Week 16, will be analyzed similar to the primary efficacy endpoint using CMH test comparing the treatment differences adjusting for the two stratification factors. Point estimates and confidence intervals will be provided similarly as well. Other binary secondary efficacy endpoints, using various definitions and at different time points, will be analyzed similarly. • The continuous secondary efficacy endpoint of change from baseline NRS at worst at Week 16 will be analyzed using analysis of covariance (ANCOVA) model which will include terms for treatment group, the stratification factors (if there are sufficient number of subjects in each stratum, otherwise the stratification factors will be dropped from the

	model), and the baseline NRS. Other continuous secondary efficacy endpoints, using various definitions and at different time points, will be analyzed similarly. • Population for the secondary efficacy endpoints will be full analysis set (FAS). Sensitivity analysis using PPAS might be performed.
CCI [redacted]	[redacted]

9.4.2. Safety Analyses

All safety analyses will be performed on the safety population.

Endpoint	Statistical Analysis Methods
Primary	Not applicable. The primary endpoint is an efficacy endpoint.
Secondary	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: • TEAEs and SAEs; • Withdrawals from treatment due to AEs; • Safety laboratory tests (eg, hematology [including coagulation panel], chemistry and lipid profiles); • Vital signs. CFB in 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.

9.4.3. Other Analyses

9.4.3.1. Analysis of Pharmacokinetic (PK) Endpoints

The PK concentration population is defined as all enrolled participants who received at least one dose of PF-06700841, PF-06826647 or PF-06650833 and in whom at least one concentration value is reported. PK concentrations will be summarized and presented with descriptive statistics. Population PK modeling may be performed with the concentration data from this study alone or combined with data from other studies. In addition, a relationship between exposures and efficacy/safety endpoints may be evaluated using population PK/PD approach. Any population analyses conducted will not be part of the clinical study report (CSR) and may be reported separately.

9.4.3.2. Patient Reported Outcome Analyses

The full analysis set (FAS) will be used for these analyses. PRO endpoints will be summarized descriptively.

Continuous PRO endpoints including CFB in HS symptom Items and CFB in DLQI score, will be analyzed using mixed models to compare the difference of active treatments with placebo participants. Missing data due to any cause including censoring due to initiation of prohibited medication will be imputed using the corresponding placebo arm, missing data in a placebo arm will be imputed using data from the placebo arm assuming data are missing at random (MAR).

9.4.3.3. PK[CCI] Unblinding Plan

If needed, a PK[CCI] 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 standard operating procedures (SOPs) for releasing randomization codes and breaking the study blind. Under this plan a group of statisticians, PK[CCI] data provider, PK[CCI] analyst and PK[CCI] 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 the last participant has been randomized. The details of the procedures will be described in the PK[redacted] Unblinding Plan for Modelling and Simulation for this study which will be finalized prior to the start of the PK[redacted] unblinding.

9.5. Interim Analyses

An interim analysis may be performed to assess efficacy and safety. Interim analysis results may be used for internal business decisions regarding future study planning. Before any interim analysis is initiated, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind as per Pfizer's SOPs will be documented and approved in an interim analysis plan. The results will only be distributed to a select list of individuals who are not part of the study team, and will be involved in the internal decision-making process in order to protect the integrity of the study. This list of individuals will be provided in the interim analysis plan. The results of the interim analysis will not enable individuals directly involved in running the study (such as investigators) to identify treatment assignments for individual participants remaining in the study. There are no plans to stop the study early for success as a result of any interim analysis.

[redacted]

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

The investigator will be responsible for the following:

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

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the IP, 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 sub investigators 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.

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 the study monitoring plan (SMP).

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

10.2. Appendix 2: Clinical Laboratory Tests

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

Table 1. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin	BUN/urea, creatinine	pH	At screening only:
Hematocrit	and Cystatin C	Glucose (qual)	FSH[b]
RBC count	Glucose	Protein (qual)	Urine drug screening
MCV	Calcium	Blood (qual)	Pregnancy test (β-hCG)[c]
MCH	Sodium	Ketones	Hepatitis B surface antigen
MCHC	Potassium	Nitrites	(HBsAg)
MPV	Chloride	Leukocyte esterase	Hepatitis B core antibody
Platelet count	Total CO_2 (bicarbonate)	Urobilinogen	(HBcAb)
WBC count	AST, ALT	Urine bilirubin	HepB reflex (HBsAb[d]), if
Total neutrophils	Total bilirubin	Microscopy and/or	applicable
(Abs)	Alkaline phosphatase	urine culture[a]	Hepatitis C antibody
Eosinophils (Abs)	Uric acid		Hepatitis C RNA, if
Monocytes (Abs)	Albumin		applicable
Basophils (Abs)	Total protein		HIVUrine myoglobin[e]
Lymphocytes (Abs)	CK		

Abbreviations: Abs = absolute; ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; CO_2 = carbon dioxide; FSH = follicle-stimulating hormone; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBsAb = hepatitis B surface antibody; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MPV = mean platelet volume; qual = qualitative; RBC = red blood cell; WBC = white blood cell.

a. Collect urine sample for central laboratory urinalysis and urine microscopy at Screening and pre-dose at Baseline. At postdose visits: urine microscopy is indicated if the urinalysis is positive for blood, nitrite, leukocyte esterase and/or protein, or there is clinical suspicion of urinary tract infection, or decrease in renal function; urine culture is performed if urinalysis is positive for nitrite and/or leukocyte esterase, or if otherwise clinically indicated.
b. For confirmation of postmenopausal status only.
c. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or institutional review board/ethics committee (IRB/EC). Serum or urine β-hCG for female participants of childbearing potential.
d. HepB reflex testing only if HBsAg negative but HBcAb positive at Screening,
e. At Screening and in case of CK >3 x ULN.

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 AEs on the CRF and for reporting serious AEs on the Clinical Trial (CT) SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the IP 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 IP 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 IP caused the event, then the event will be handled as "related to IP" 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) ***plus*** an additional 90 days (a spermatogenesis cycle):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual or homosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use contraception/barrier as detailed below.
    - Agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.
- Use of an additional highly effective contraceptive method with a failure rate of <1% per year as described below in Section 10.4.4 for a female partner of childbearing potential.

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), (preferably) 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 (except for sexual abstinence). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

10.4.3. Woman of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female:

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

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

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

10.4.4. Contraception Methods

Highly Effective Methods 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 or bilateral tubal ligation.

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.

§ Use of implantable progestogen-only hormone contraception associated with inhibition of ovulation **with an effective barrier method** (as described below) is required for female participants randomized to receive PF-06650833/matching placebo.

Highly Effective Methods That Are User Dependent

One of the following effective barrier methods must be used in addition to the highly effective methods listed below that are user dependent except for sexual abstinence:

- Male or female condom with or without spermicide;

- Cervical cap, diaphragm, or sponge with spermicide;

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

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.
3. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

§ All contraceptives containing ethinyl estradiol, being a CYP 1A2 inhibitor, are prohibited in female participants randomized to receive PF-06826647/matching placebo. Refer to Appendix 10.9.

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 IP; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the IP;
    - 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 IP 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 IP, 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 IP.

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]

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

Potential Cases of Drug-Induced Liver Injury

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

In the majority of DILI cases, elevations in AST and/or 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: Guidelines for Safety Monitoring and Discontinuation

These guidelines for participant safety monitoring and discontinuation are to be applied to all participants in the study. Additional individual participant monitoring is at the discretion of the investigator and dependent on any perceived safety concerns. Unscheduled clinical labs may be obtained at any time during the study to assess such concerns, and a participant may be withdrawn at any time at the discretion of the investigator.

Monitoring

The following laboratory abnormalities require re-testing within 1 week (ideally within 48 hours):

- Neutrophil counts <1000 neutrophils/mm^3;
- Lymphocyte counts <500 lymphocytes/mm^3;
- Platelet counts <50,000 platelets/mm^3;
- Any single AST and/or ALT elevation ≥3 times the ULN (repeat laboratory testing should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, PT [prothrombin time] with INR [international normalized ratio], and alkaline phosphatase), regardless of the total bilirubin. (Please note that 3 times the ULN increases in ALT, AST need confirmation on separate blood draw before undertaking thorough evaluation for liver injury); note: re-testing for AST and/or ALT is expected to be completed within 48 hours;
- Any single hemoglobin value <8.0 g/dL or one that drops 2 gm/dL below baseline;
- For women of child-bearing potential with any positive urine beta-human chorionic gonadotrophin (β-hCG) test, the participant will have investigational product interrupted and a serum sample submitted to the central laboratory for β-hCG testing;
- CK >3 x ULN (this also triggers urine myoglobin).

Discontinuation

Potential Cases of Decreased eGFR

- If an individual participant demonstrates CONCOMITANT SCr-based AND serum Cystatin C-based eGFR decline of ≥30% (See Section 8.2.5.1) 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 SCr 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 SCr.

- All relevant test results will be forwarded to Sponsor Medical Monitor for review immediately upon receipt by the PI.

Adverse Events

The sponsor's Clinical team should be consulted as soon as possible and participants may be discontinued from treatment if any of the following occur during the study:

- Serious infections defined as any infection (viral, bacterial, and fungal) requiring parenteral antimicrobial therapy, hospitalization for treatment, or meeting other criteria that require the infection to be classified as serious AE;

- Other serious or severe AEs, at the discretion of the investigator or sponsor;

- Participants triggering criteria for suicidal ideation and behavior as described in Section 8.2.7.

All of the following laboratory abnormalities require discontinuation if they are confirmed (confirmation through re-testing should occur within one week [ideally within 48 hours]):

- Two sequential absolute neutrophil counts $<1.0 \times 10^9$/L ($<1000/mm^3$);

- Two sequential hemoglobin values <8.0 g/dL; <4.96 mmol/L; <80 g/L;

- Two sequential platelet counts $<50 \times 10^9$/L ($<50,000/mm^3$);

- Two sequential lymphocyte counts $<500/mm^3$; $<0.5x10^9$/L;

- Two sequential AST or ALT elevation ≥3 times the ULN with at least one total bilirubin value ≥1.5 times the upper limit of normal;[a] note: re-testing for AST and/or ALT is expected to be completed within 48 hours:

  - Two sequential AST or ALT elevation ≥3 times the ULN accompanied by signs or symptoms consistent with hepatic injury;[a]

  - Two sequential AST or ALT elevation ≥5 times the upper limit of normal, regardless of total bilirubin or accompanying signs or symptoms;[a]

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

  - Participants with QTc prolongation ≥30 msec from the baseline and >450 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG for greater than 4 hours.

  a. In each case, there is a need for additional investigations, such as review of ethanol, recreational drug and dietary supplement consumption; testing for acute hepatitis A, B or C infection and biliary tract imaging should be promptly discussed with the Pfizer medical monitor or designee.

C-SSRS Assessment

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

10.9. Appendix 9: Prohibited Concomitant Medications

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

CYP1A2, CYP3A and CYP2D6 Inhibitors

CYP1A2
Ciprofloxacin
Clinafloxacin
diethyl-dithiocarbamate
Enoxacin
Etintidine
Fluvoxamine
Idrocilamide
Methoxsalen
Mexiletine
Oltipraz
Oral contraceptives (**only those containing ethinyl estradiol**)
Phenylpropanolamine
Pipemidic acid
Propafenone
Propranolol
Rofecoxib
Troleandomycin
Vemurafenib
Zafirlukast

CYP2D6
Buproprion
Cinacalcet
Dacomitinib
Dronedarone
Duloxetine
Eliglustat
Fluoxetine
Mirabegron
Moclobemide
Paroxetine
Quinidine

CYP1A2, CYP3A4, Inducers

CYP1A2
Carbamazepine
Efavirenz
Phenytoin
Rifampin
Ritonavir

OCT2/MATE substrates

Dofetilide

BCRP Inhibitors
Cyclosporine
Elacridar (FG120918)
Eltrombopag
Gefitinib

BCRP Substrates

Rosuvastatin

P-gp substrates with narrow TI:
Digoxin

CYP1A2, CYP3A and CYP2D6 Inhibitors	**CYP1A2, CYP3A4, Inducers**	**OCT2/MATE substrates**
Rolapitant		
Telithromycin		
Terbinafine		
Tipranavir		

CYP 3A4	***CYP3A4***
	Avasimibe
Amiodarone	Barbiturates
Amprenavir	Bosentan
Aprepitant	Carbamazepine
Atazanavir	Efavirenz
Boceprevir	Enzalutamide
Casopitant	Etravirine
Cimetidine	Genistein
Ciprofloxacin	Lersivirine
Clarithromycin	Lopinavir
Cobicistat	Mitotane
Conivaptan	Modafinil
Crizotinib	Nafcillin
Cyclosporine	Phenobarbital
Danoprevir	Phenytoin
Darunavir	Rifabutin
Delavirdine	Rifampin
Diltiazem	Ritonavir
Dronedarone	Semagacestat
Elvitegravir	St. John's Wort
Erythromycin	Talviraline
Faldaprevir	Teriflunomide
Fluconazole	Thioridazine
Gestodene	Troglitazone
Grapefruit Juice***, marmalade	
Idelalisib	
Imatinib	
Indinavir	
Isavuconazole	
Itraconazole	
Ketoconazole	
Lopinavir	
Mibefradil	
Mifepristone (RU486)	
Nefazodone	

CYP1A2, CYP3A and CYP2D6 Inhibitors	CYP1A2, CYP3A4, Inducers	OCT2/MATE substrates
Nelfinavir		
Netupitant		
Nilotinib		
Norfloxacin		
Norfluoxetine		
Posaconazole		
Ritonavir		
Saquinavir		
Schisandra sphenanthera		
Telaprevir		
Telithromycin		
Tipranavir		
Tofisopam		
Troleandomycin		
Verapamil		
Viekira pak		
Voriconazole		

All prohibited drugs that are CYP3A inhibitors require at least a 7 day or 5 half-lives (whichever is longer) prior to the first dose of study drug. Note: Amiodarone requires discontinuation at least 290 days (~5 half-lives, half-life averages ~58 days) prior to the first dose of IP.

All prohibited drugs that are CYP3A inducers require at least a 28 day or 5 half-lives (whichever is longer) prior to the first dose of IP.

***It is recommended that subjects avoid consumption of grapefruit juice exceeding 8 ounces (~240 mL) total in a day while in the study.

In a situation where appropriate medical care of a subject requires the use of a prohibited CYP3A inhibitor or inducer:

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

Concomitant Medications to be Used with Caution

BCRP Substrates (Use with caution)*	
Pibrentasvir	
Glecaprevir	

*As per their respective labels, the concentration of these compounds may increase when co-administered with BCRP inhibitors (eg, PF-06650833, PF-06700841).

Table 2 Common Drugs Known to Cause Torsades de Pointes[11,18]	
Class	**Examples**
Antiarrhythmics	Disopyramide, procainamide, quinidine, sotalol
Macrolides	Azithromycin, clarithromycin, erythromycin
Fluoroquinolones	Ciprofloxacin, levofloxacin, moxifloxacin
Antifungals	Fluconazole, ketoconazole, pentamidine, voriconazole
Antipsychotics	Haloperidol, thioridazine, ziprasidone
Antidepressants	Citalopram, escitalopram,
Antiemetics	Dolasetron, droperidol, granisetron, ondansetron
Opioids	Methadone
Miscellaneous	Cocaine, cilostazol, donepezil

From: https://www.ptcommunity.com/system/files/pdf/ptj4207473.pdf

10.10. Appendix 10: 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 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 S_{cys} is ≤0.8 mg/dL:

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

If female and S_{cys} is >0.8 mg/dL:

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

If male and S_{cys} is ≤0.8 mg/dL:

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

If female and S_{cys} is >0.8 mg/dL:

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

10.11. Appendix 11: Columbia Suicide Severity Rating Scale (C-SSRS)[19]

C-SSRS for Screening Visit

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

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

Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

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

C-SSRS for post-baseline visits

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

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐
Suicide:	**Yes No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

10.12. Appendix 12: Abbreviations

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

Abbreviation	Term
AA	alopecia areata
Abs	absolute
ACPA+	anti-anticitrullinated protein antibody positive
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
AN	abscess and inflammatory nodule
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{24}	area under the curve at 24 hours
AUC_{inf}	area under the curve time zero to infinity
AV	atrioventricular
BA	bioavailability
BBS	Biospecimen Banking System
BCG	Bacille Calmette Guérin
BCRP	breast cancer resistance protein
β-hCG	beta-human chorionic gonadotropin
BID	twice daily
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BSEP	bile salt export pump
BUN	blood urea nitrogen
$C_{av,ss}$	average amount at steady state
CFB	change from baseline
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatinine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	apparent clearance
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CrI	credible interval

Abbreviation	Term
CRO	contract research organization
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CT	clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	clinical trial management system
CV	cardiovascular
CYP	cytochrome P450
DCT	data collection tool
DILI	drug-induced liver injury
DLQI	Dermatology Life Quality Index
CCI	[redacted]
dn	dose normalized
DNA	deoxyribonucleic acid
DU	dispensable unit
EBV	Epstein-Barr virus
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDP	exposure during pregnancy
EFD	embryofetal developmental
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	End of Study
EPO	epogen
ePRO	electronic patient reported outcomes
CCI	[redacted]
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
CCI	[redacted]
FAS	full analysis set
FIH	first in human
FSH	follicle-stimulating hormone
f_u	fraction of drug unbound in plasma
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP	Good Laboratory Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody

Abbreviation	Term
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HiSCR	hidradenitis suppurativa clinical response
HIV	human immunodeficiency virus
HRQoL	health-related Qaulity of Life
HRT	hormone replacement therapy
HS	hidradenitis suppurativa
CCI	[redacted]
IB	investigator's brochure
IBD	inflammatory bowel disease
IC	inhibitory concentration
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IFN	interferon
IGRA	Interferon Gamma Release Assay
IHS4	International Hidradenitis Suppurativa Severity Score System
IL	interleukin
IMP	investigational medicinal product
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IP manual	investigational product manual
IR	immediate release
IRAK4	IL -1 receptor associated kinase 4
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
JAK1	Janus Kinase 1
KDIGO	Kidney Disease: Improving Global Outcomes
LASER	light amplification by stimulated emission of radiation
LBBB	left bundle branch block
LFT	liver function test
LLOQ	lower limit of quantification
MAD	multiple ascending dose
MAR	missing at random
MATE	multidrug and toxin extrusion transporter
MCH	mean corpuscular hemoglobin

Abbreviation	Term
MCHC	mean corpuscular hemoglobin concentration
MCS	mental component scores
MCV	mean corpuscular volume
MDR1	multidrug resistant protein 1
MMR	Measles Mumps Rubella
MPV	mean platelet volume
MR	modified release
MRI	magnetic resonance imaging
CCI	[redacted]
MRP	multidrug resistance-associated protein
msec	millisecond
MTX	methotrexate
N/A	not applicable
NIMP	noninvestigational medicinal product
NOAEL	no-observed-adverse-effect level
NRS	numeric rating scale
NRS-11	Numerical Rating Scale-11
NSAIDs	nonsteroidal anti-inflammatory drugs
NTCP	sodium/taurocholate co-transporting polypeptide
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
PASI	Psoriasis Area and Severity Index
PBMC	peripheral blood mononuclear cell
PCD	primary completion date
PCP	primary care physician
PCR	polymerase chain reaction
PCS	physical component score
PD	pharmacodynamic(s)
PE	physical exam
PGA	Patient's Global Assessment
CCI	[redacted]
CCI	[redacted]
PI	principal investigator
PK	pharmacokinetic(s)
PPAS	per protocol analysis set
PPD	Purified Protein Derivative
PRN	as needed
PRO	patient reported outcome
PsO	psoriasis
PT	prothrombin time
PVC	premature ventricular contraction/complex

Abbreviation	Term
QD	once daily
QID	four times a day
QoL	quality of life
QFT-plus	QuantiFERON®-TB Gold Plus (QFT-plus)
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
QW	once weekly
qual	qualitative
RA	rheumatoid arthritis
RBC	red blood cell
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SCr	serum creatinine
SDAI	simplified disease activity index
SDD	sprayed dried dispersion
[redacted]	[redacted]
SMP	study monitoring plan
SoA	schedule of activities
SOC	system organ class
SOP	standard operating procedure
SRSD	single reference safety document
SSID	screening number
SToD	study team on demand
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	half-life
TB	tuberculosis
TBili	total bilirubin
TBNK	lymphocyte subsets (T cells, B cells, and NK cells)
TdP	torsade de pointes
TEAEs	treatment emergent adverse events
TH	T-helper
TID	three time a day
TLR	tool-like receptor
T_{max}	time to maximal concentration
TNF	tumor necrosis factor
TYK2	tyrosine kinase 2
UGT	5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
US	United States
UVA	Ultra violet A

Abbreviation	Term
VAS	visual analog scale
VTE	venous thromboembolic events
Vz/F	volume of distribution
WBC	white blood cell
WOCBP	woman of childbearing potential

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