A PHASE 1, OPEN-LABEL, FIXED-SEQUENCE, 2-PERIOD STUDY TO ESTIMATE THE EFFECT OF MULTIPLE DOSE ABROCITINIB ON THE PHARMACOKINETICS OF SINGLE DOSES OF CAFFEINE, EFAVIRENZ, AND OMEPRAZOLE IN HEALTHY PARTICIPANTS

Study Intervention Number:	PF-04965842
Study Intervention Name:	Abrocitinib
US IND Number:	123554
EudraCT Number:	N/A
ClinicalTrials.gov ID:	N/A
Protocol Number:	B7451092
Phase:	1

Brief Title: A Phase 1 Study to Estimate the Effect of Multiple Dose Abrocitinib on the PK of Caffeine, Efavirenz, and Omeprazole in Healthy Participants

Document History

Document	Version Date
Original protocol	28 July 2021

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1. PROTOCOL SUMMARY

1.1. Synopsis

Brief Title: A Phase 1 Study to Estimate the Effect of Multiple Dose Abrocitinib on the PK of Caffeine, Efavirenz, and Omeprazole in Healthy Adult Participants

Rationale

The purpose of the study is to evaluate the effect of abrocitinib on the in vivo PK of sensitive CYP1A2, 2B6 and 2C19 substrates, caffeine, efavirenz, and omeprazole, respectively.

Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
• To estimate effect of multiple dose abrocitinib on the PK of single, oral doses of caffeine, efavirenz and omeprazole in healthy participants.	• AUC_{inf} (if applicable, otherwise AUC_{last}) of caffeine, efavirenz and omeprazole.
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of abrocitinib when co administered with single doses of caffeine, efavirenz and omeprazole.	• Vital signs, laboratory tests and AEs.
CCI [redacted]	[redacted]
[redacted]	[redacted]

Overall Design

Brief Summary

This is a Phase 1, open-label, multiple dose, single fixed-sequence, 2-period study to evaluate the effect of abrocitinib on the PK of caffeine, efavirenz and omeprazole in healthy adult participants. A total of approximately 13 healthy male and/or female participants will be enrolled in the study to obtain at least 12 evaluable participants who complete the study. Participants who withdraw from the study or are considered non-evaluable may be replaced at the discretion of the sponsor.

Participants will be screened within 28 days of the first dose of study intervention. Participants will have a phone contact 3 days prior to Day 1 dosing (Day -3) in Period 1 as a reminder to abstain from caffeine-containing products. Participants will be admitted to the

CRU at least 24 hrs prior to Day 1 dosing (Day -1) in Period 1. Participants will remain in the CRU for a total of 15 days and 14 nights.

Participants will have a telephone contact between 28-35 calendar days after the last administration of the investigational product.

Number of Participants

A total of approximately 13 healthy male and/or female participants will be enrolled in the study to obtain at least 12 evaluable participants who complete the study.

Note: "Enrolled" means a participant's, or his or her legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and screening. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration

In Period 1, all the participants will receive single doses of the probe drugs, including caffeine 100 mg, efavirenz 50 mg and omeprazole 10 mg, together on Day 1. After 3 days of PK sampling in Period 1, Period 2 will immediately follow with no washout. The Day 1 of Period 2 begins on the fourth day following the start of Period 1. In Period 2, participants will receive abrocitinib 200 mg QD on Day 1-10. Participants will receive single doses of the probe drugs (caffeine 100 mg, efavirenz 50 mg and omeprazole 10 mg together) again on Day 8, and omeprazole 10 mg alone on Day 2, within approximately 5 minutes after administration of abrocitinib 200 mg on the morning of the respective day.

The total planned duration of participation, from the Screening visit to the last Follow-up phone call, is approximately up to 11 weeks.

Data Monitoring Committee or Other Independent Oversight Committee: No

Statistical Methods

Natural log-transformed parameters (AUC_{inf}, AUC_{last} [redacted]) will be analyzed using a mixed effect model with treatment as a fixed effect and subject as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CI for the ratios.

1.2. Schema (Not Applicable)

1.3. Schedule of Activities

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.

Visit Identifier[a]	Screening	Period 1				Period 2						Follow-Up Phone Call	Early Termination/ Discontinuation
Days Relative to Day 1	**Day -28 to Day -4**	**Day -3**	**Day -1[o]**	**Day 1**	**Day 2-3**	**Day 1**	**Day 2**	**Day 3-7**	**Day 8**	**Day 9-10**	**Day 11**	**28-35 Days[b]**	
Informed consent	X												
Phone contact reminder[p]		X											
CRU confinement			X	→	→	→	→	→	→	→	X		
Inclusion/exclusion criteria	X		X										
Medical, drug, tobacco and alcohol history	X		X										
Physical exam *(including height and weight)*[c]	X												
Safety laboratory	X		X								X		X
Demography	X												
Pregnancy test *(WOCBP only)*	X		X								X		X
Contraception check	X		X								X	X	X
FSH	X												
Urine drug testing	X		X										
TB screening[d]	X												
Single 12-Lead ECG[e]	X			X							X		X
BP, pulse rate and temperature[e]	X			X							X		X
HIV, HBsAg, HCVAb and HBcAb[f]	X												
COVID-19 questionnaire[g]	X		X										
COVID-19 testing[h]	X		X										
COVID-19 check temperature[i]	X		X	X	X	X	X	X	X	X	X		X
C-SSRS	X		X			X			X		X		X

Visit Identifier[a]	Screening	Period 1				Period 2						Follow-Up Phone Call	Early Termination/ Discontinuation
Days Relative to Day 1	**Day -28 to Day -4**	**Day -3**	**Day -1[o]**	**Day 1**	**Day 2-3**	**Day 1**	**Day 2**	**Day 3-7**	**Day 8**	**Day 9-10**	**Day 11**	**28-35 Days[b]**	
Abrocitinib QD administration[j]						X	X	X	X	X			
Caffeine, efavirenz, and omeprazole administration[k]				X					X				
Omeprazole administration only[l]							X						
PK blood sampling[m]				X	X		X		X	X	X		X
CCI [redacted]													
Serious and nonserious AE monitoring	X		→	→	→	→	→	→	→	→	X	X	X
Prior/concomitant treatment assessment	X		→	→	→	→	→	→	→	→	X	X	X
CRU discharge											X		

Abbreviations used in this table may be found in Appendix 8.

a. **Visit Identifier:** Day relative to start of study intervention (Day 1).
b. **28-35 Days:** Participants will have a telephone contact between 28-35 calendar days after the last administration of the investigational product.
c. **Physical exam** *(including height and weight)***:** Complete physical exam could be done at screening or admission Period 1. Brief physical exam to be done only in case of a finding at previous exam or new/open AE if applicable, at the discretion of the investigator.
d. **TB screening:** TB screening will utilize IGRA. Details of eligibility are described in Appendix 2.
e. **Single 12-Lead ECG, BP, pulse rate and temperature:** ECG and vital signs will be collected at screening, before dosing on Day 1 of period 1, and on Day 11 of period 2.
f. **HIV, HBsAg, HCVAb and HBcAb:** All participants will undergo screening for Hepatitis B and Hepatitis C for eligibility. Please refer to Appendix 2 for testing algorithm, reflex testing, and full eligibility criteria.
g. **COVID-19 questionnaire:** Check exposure to positive subject, residence or travel in area of high incidence and COVID-19 related signs and symptoms. To be done at each visit.
h. **COVID-19 testing:** The testing for COVID-19 pathogen by PCR will be performed at each visit. For participants admitted for residence, a subsequent COVID-19 test will be performed after 4 days (ie, upon completion of 4×24 hours in house), or if they develop COVID-19 like symptoms.
i. **COVID-19 check temperature:** To be done at least daily during residence.
j. **Abrocitinib QD administration:** The dosing of abrocitinib will be administered at approximately 08:00 ± 2 hours.
k. **Caffeine, efavirenz, and omeprazole administration:** Participants will be dosed with caffeine, efavirenz, and omeprazole following an overnight fast of at least 10 hours at approximately 08:00 ± 2 hours. On the day of co administration abrocitinib, abrocitinib will be administered first. After swallowing the abrocitinib dose, caffeine, efavirenz, and omeprazole should be administered within approximately 5 minutes.
l. **Omeprazole administration only:** Participants will be dosed with omeprazole following an overnight fast of at least 10 hours, within approximately 5 minutes after the abrocitinib administration.
m. **PK blood sampling:** Refer to Table 1 for detailed PK blood sampling schedules.
C [redacted]
C

Visit Identifier[a]	Screening	Period 1				Period 2						Follow-Up Phone Call	Early Termination/ Discontinuation
Days Relative to Day 1	Day -28 to Day -4	Day -3	Day -1[o]	Day 1	Day 2-3	Day 1	Day 2	Day 3-7	Day 8	Day 9-10	Day 11	28-35 Days[b]	

o. **Day -1:** Participants will be admitted to the CRU at least 24 hrs prior to Day 1 dosing (Day -1) in Period 1.
p. **Phone contact reminder:** Participants will have a phone contact 3 days prior to Day 1 dosing (Day -3) in Period 1 as a reminder to abstain from caffeine-containing products. Please refer to Section 5.3.2 for the list of caffeine-containing products.

Table 1. Pharmacokinetics Sampling Schema

Study Period	**1**													**2**	**2**				**2**															
Study Day	**1**											**2**	**3**	**1**	**2**				**8**												**9**	**10**	**11**
Hours Before/After Dose	**0**	**0.5**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**24**	**48**	**72**	**0**	**1**	**3**	**6**	**8**	**0**	**0.5**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**24**	**48**	**72**
Caffeine, efavirenz, and omeprazole administration	X																			X													
PK blood sampling for caffeine, efavirenz, and omeprazole[b]	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X[a]						X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Abrocitinib QD administration[c]														X	X					X											X	X	
Omeprazole administration															X																		
PK blood sampling for omeprazole only															X[a]	X	X	X	X														

a. PK sample will be collected before the abrocitinib dose.

b. For 48 and 72 hour samples, only efavirenz will be analyzed.

c. Note that abrocitinib is administered QD and this table only depicts administration on days with pharmacokinetic samples.

2. INTRODUCTION

Abrocitinib (also referred to as PF-04965842) is an orally bioavailable potent JAK1 inhibitor with good selectivity over the broader kinome being developed for the treatment of AD.[1]

2.1. Study Rationale

The purpose of the study is to evaluate the effect of abrocitinib on the in vivo PK of sensitive CYP1A2, 2B6 and 2C19 substrates, caffeine, efavirenz, and omeprazole, respectively.

2.2. Background

2.2.1. Nonclinical Pharmacology

Abrocitinib inhibits cytokines implicated in AD pathogenesis. For example, in vitro, abrocitinib inhibits IL-4 and IL-13 signaling in B cells, monocytes and keratinocytes, IL-4 signaling in T cells and IL-31 signaling in THP-1 cells. Abrocitinib also inhibits IL-22 in keratinocytes and IFN-α, IFN-γ, IL-6 and other JAK1 dependent cytokines in PBMCs and human whole blood. The primary human metabolites of abrocitinib (M1 and M2) showed a profile of cytokine inhibition, via JAK1-dependent pathways, similar to the parent compound abrocitinib, while M4 was pharmacologically inactive. In AIA rats, abrocitinib exhibited a significant and maximal inhibition of disease for this model as well as significant inhibition of cytokine dependent STAT phosphorylation in ex vivo stimulated whole blood. Significant abrocitinib inhibition (>50%) of binding or enzyme activity of MAO-A and KDR kinase (VEGFR2) was observed, with IC_{50} values that were respectively 4.8× and 1.0× the unbound human C_{max} at a clinical dose of 200 mg QD.

In vitro safety pharmacology studies were conducted to assess potential hERG (GLP) and Nav1.5 (non-GLP) inhibition and the IC_{50} was 76× and 240×, respectively, at the unbound human C_{max}. These ion channel in vitro assessments satisfy ICH S7A/B guidelines. In the broad ligand profile screen, less than 50% inhibition of calcium channel binding was observed. Overall, the nonclinical in vitro data for abrocitinib (and M1, M2, and M4) contribute to the weight of evidence for no significant effects at clinically relevant concentrations on the primary cardiac ion channels (eg, hERG, Nav1.5, or Cav1.2) generally considered to be most important for risk assessment of QT prolongation.

In vivo safety pharmacology studies were conducted to assess potential effects on the nervous, cardiovascular, and pulmonary systems. Abrocitinib produced lower locomotor activity (horizontal and vertical movements) and body temperature in rats and increases in HR and diastolic BP in cynomolgus monkeys. No other effects on parameters in the FOB were observed or on the telemetry-based activity measure in the rat or cynomolgus monkey cardiovascular safety pharmacology studies were observed. No primary QT signals, including no QTc prolongation, were observed in the cardiovascular safety pharmacology study in cynomolgus monkeys.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

Plasma profiling from the [^{14}C]abrocitinib human mass balance study indicated unchanged abrocitinib as the most prevalent circulating species (26%), with 3 major and more polar

mono-hydroxylated metabolites identified. M1, M2, and M4 are not unique to humans, and were shown to have sufficient exposures at NOAEL doses in rats (rat/human AUC_{24} ratios ≥1) relative to the projected highest therapeutic human dose of 200 mg daily.

In vitro and in vivo metabolite profiling suggested that the primary clearance mechanism for abrocitinib was CYP-mediated oxidation, with CYP2C19 the primary contributor at approximately 50%. CYP metabolism played a minor role (<25%) in the clearance of metabolites M1, M2 and M4. Renal excretion of parent drug was limited in the mouse, rat and humans, while urinary excretion was the major route of elimination for M1, M2, and M4.

Abrocitinib, M1, M2, and M4 were not significant competitive inhibitors of CYP enzymes, but showed varying weak TDI activities versus CYP3A, CYP2C19 and CYP2D6. Abrocitinib exhibited a weak potential to induce CYP1A2, CYP3A4 and CYP2B6. M1, M2, and M4 did not induce CYP3A4 enzyme activity or mRNA. M1 and M2 showed a weak potential to induce CYP1A2 and CYP2B6. Clinical results with midazolam as a victim indicated no significant risk of interaction through inhibition or induction of CYP3A after abrocitinib administration.

Abrocitinib, M1, M2, and M4 were not significant inhibitors of the major UGT enzymes or SULT enzymes. Clinical results with ethinyl estradiol as a victim indicated no significant risk of UGT or SULT inhibition by abrocitinib and its metabolites.

Abrocitinib was not a substrate for OATP1B1 or OATP1B3, nor inhibited these transporters. Abrocitinib did not inhibit OAT1, OCT2, or bile salt export pump, but inhibited OAT3, P-gp, BCRP, OCT1, MATE1, and MATE2K. M1, M2, and M4 did not inhibit P-gp, OCT2, and OAT1. M2 and M4 did not inhibit OATP1B1 and OATP1B3. M1, M2, and M4 inhibited BCRP, MATE1, MATE2K, and OAT3. Clinical results showed abrocitinib co-administration increased dabigatran exposure <2 fold, indicative of the inhibition of dabigatran etexilate efflux by P-gp, and showed no significant effect on the exposure of rosuvastatin (BCRP, OAT3 probe substrate) or metformin (OCT2, MATE1/2K, OCT1 probe substrate).

Overall risk as a victim of a transporter interaction from M1, M2, and M4 is considered low. M1, M2 and M4 were substrates of OAT3, but not MATE1, MATE2K, OAT1 or OCT2. Clinical results with probenecid (an OAT3 inhibitor) coadministration significantly increased exposure of M1, M2, and M4, but had no effect on abrocitinib exposure.

2.2.3. Nonclinical Safety

Abrocitinib was assessed in a series of nonclinical toxicity studies. In repeat-dose toxicity studies, abrocitinib was administered chronically to rats and cynomolgus monkeys in studies up to 6 and 9 months in duration, respectively. In these toxicity studies, abrocitinib-related findings were generally consistent with the expected immunomodulatory pharmacology of abrocitinib, no unique or unanticipated immunotoxicities were noted after abrocitinib administration, and most abrocitinib-related effects had reversed by the end of a 12-week recovery phase.

Target organs identified included the immune and hematolymphopoietic systems, bone, liver, kidney, and skin. In addition, effects on HR, diastolic BP, locomotor activity, and body temperature were observed in the safety pharmacology studies. Administration of abrocitinib was also associated with emesis in cynomolgus monkeys and an increase in small cytoplasmic vacuolation of brown adipose tissue in rats. No evidence of proliferative or neoplastic lesions was noted in the chronic toxicity studies.

Abrocitinib is not mutagenic or clastogenic based on the results of a series of in vitro and in vivo tests for gene mutations and chromosomal aberrations.

Abrocitinib did not affect the male reproductive system, including fertility or spermatogenesis, but did result in reversible decreased female fertility. Effects on female fertility (decreased fertility index, corpora lutea, implantation sites) and increased post-implantation loss were observed in rats at 70 mg/kg/day and 30 mg/kg/day with exposures 29× and ≥11, respectively, the unbound human AUC at the clinical dose of 200 mg QD and were fully reversible following a 1-month recovery.

Abrocitinib did not cause malformations in rats or rabbits.

Additionally, data from animal studies revealed that abrocitinib is not genotoxic, and does not have an impact on male fertility, and no histopathological changes were noted in the testes and epididymides with abrocitinib administration for up to 6 and 9 months at doses up to 70 and 75 mg/kg/day in rats and cynomolgus monkeys, respectively, and corresponding exposures were 26× and 10× the unbound AUC at the human clinical dose of 200 mg. Furthermore, in vivo data show that abrocitinib does not have phototoxicity potential.

2.2.4. Clinical Overview

2.2.4.1. Summary of Safety Data from Completed Studies

Based on the clinical experience with abrocitinib and its mechanism of action, the potential risks of treatment with JAK inhibitors include: (1) viral reactivation; (2) serious infection and opportunistic infections; (3) malignancy and lymphoproliferative disorders; (4) decreased lymphocyte counts; (5) decreased neutrophil counts; (6) decreased platelets; (7) alterations in the lipid profile; and (8) venous thromboembolism (deep venous thrombosis/pulmonary embolism).

In the completed Phase 1 and 2 studies in healthy participants, participants with psoriasis and participants with AD, abrocitinib was generally safe and well tolerated.

In the completed Phase 1 studies in healthy participants receiving single doses of abrocitinib up to 800 mg and multiple doses up to 200 mg BID or 400 mg QD, the most commonly reported AEs were diarrhea, nausea, vomiting, headache, acne, and dizziness. Following single or multiple dose of abrocitinib, most reported TEAEs were mild or moderate in severity. In study B7451001, during the single ascending dose phase, 1 participant in the placebo group had maximum QTcF interval of 450 <480 msec, and 1 participant in the abrocitinib 800 mg treatment group had maximum QTcF interval increase from baseline of

30 to <60 msec. In the multiple ascending dose phase, 3 participants (1 each in the placebo, abrocitinib 30 mg QD, and 100 mg QD treatment groups) had maximum QTcF interval of 450 <480 msec, and 2 participants in the abrocitinib 200 mg BID treatment group had maximum QTcF interval increase from baseline of 30 to <60 msec.

In the completed Phase 2 study in participants with moderate to severe psoriasis (B7451005), the most frequently reported AEs across the abrocitinib treatment groups (200 mg BID, 200 mg QD, and 400 mg QD) were nausea, followed by headache. Other commonly reported AEs include neutropenia and neutrophil counts decreased, thrombocytopenia and platelet count decreased. One of the participants in the 200 mg QD group with an AE categorized as infections and infestations was reported as having VIIth nerve paralysis (Bell's palsy) and later developed herpes zoster (shingles). The incidence of normal and abnormal ECG recordings was similar across all treatment groups at each time point. None of the abnormal ECG recordings were determined to be clinically significant by the investigator.

In the completed 12-week Phase 2b study (B7451006) in participants with AD, AEs and SAEs were numerically higher in participants receiving abrocitinib (10, 30, 100, and 200 mg QD) compared to placebo, but did not appear to increase with dose. The most common AEs were in the infections and infestations, skin and subcutaneous tissue disorders and gastrointestinal disorders SOC, and the majority of the AEs were mild. The most commonly reported TEAEs across all the treatment groups were dermatitis atopic (38 events), and viral upper respiratory tract infection (33 events). The most frequently reported treatment related TEAE was nausea. There were 2 cases of nonserious herpes zoster, one in the 10 mg group (not treatment-related), and one in the 30 mg group (treatment-related). There were 2 participants (doses of ≥100 mg QD) with treatment related SAEs reported, the SAEs were eczema herpeticum and pneumonia. One participant randomized to the abrocitinib 10 mg group reported an SAE of malignant melanoma. Dose dependent mean platelet count decreases from baseline were observed with a nadir at Week 4. At Week 4 the mean platelet count and the 90% CI were within the normal reference range for both the 100 mg dose and 200 mg dose. In these treatment groups, the mean platelet count increased towards baseline after Week 4. There were no clinically significant findings in vital signs or physical examinations. Most of the ECG results were normal. The incidence of normal and abnormal ECG recordings was similar between abrocitinib and placebo groups at each time point.

In the completed 12-week Phase 3 study (B7451012) in adult and adolescent participants aged 12 years and older with moderate to severe AD, the most frequent all-causality TEAEs that occurred in ≥5% of participants of any treatment group (100 mg QD and 200 mg QD) were nausea, nasopharyngitis, upper respiratory tract infection, headache, and dermatitis atopic. Nausea was the most frequently reported treatment-related TEAE with ≥5% higher incidence in the abrocitinib treatment groups compared with the placebo group. Majority of TEAEs reported were mild to moderate in severity.

Similarly, safety data from the completed 12-week Phase 3 study (B7451013) in adult and adolescent participants aged 12 years and older with moderate to severe AD, have reported similar TEAEs to the ones observed in study B7451012. The safety data reported in this

study showed that the most frequent all-causality TEAEs that occurred in ≥5% of participants of any treatment group (100 mg QD and 200 mg QD) were nausea, nasopharyngitis, upper respiratory tract infection, headache, and dermatitis atopic. Nausea was the most frequently reported treatment-related TEAE with ≥5% higher incidence in the abrocitinib 200 mg treatment group compared with the placebo group. Majority of TEAEs reported were mild to moderate in severity.

2.2.4.2. Summary of Abrocitinib Pharmacokinetics, Metabolism and In Vitro Enzymology

2.2.4.2.1. Single and Multiple Dose Pharmacokinetics

Abrocitinib was absorbed rapidly following single oral solution/suspension doses of 3 mg to 200 mg with median time to T_{max} observed less than 1 hour (ranging from 0.55 to 0.77 hours), and more slowly at the higher doses with median T_{max} of 1.5 and 4.0 hours for the 400 mg and 800 mg doses, respectively (Study B7451001). Following attainment of C_{max}, the disposition of abrocitinib generally showed a monophasic decline at the lower doses of 3 to 30 mg (mean apparent $t_{½}$ of 1.9 to 2.5 hours) while a biphasic decline was observed at doses of 100 to 800 mg with a mean $t_{½}$ of 3.6 to 4.9 hours. Plasma abrocitinib C_{max} appeared to increase proportionally across the entire dose range from 3 mg to 800 mg, while increases in AUC_{inf} were greater than proportional at doses of 400 and 800 mg. For the 2-fold doses increase between 200 to 400 mg and between 400 to 800 mg, the mean AUC_{inf} values in Western participants in this study appeared to increase approximately 3.5- and 2.7-fold, respectively.

On Day 10 of multiple-dose administration, abrocitinib was absorbed rapidly with median T_{max} of about 1 hour or less (ranging from 0.50-1.05 hours) across the entire range of doses, from a total daily dose of 30 mg (30 mg QD) up to 400 mg (200 mg BID or 400 mg QD). Following attainment of C_{max}, the disposition of abrocitinib was consistent with that observed following single dose administration, showing a biphasic decline following all but the lowest dose and a mean $t_{½}$ of about 2.8 to 5.0 hours. Plasma C_{max} and AUC_{tau} both appeared to show a trend towards greater than proportional increases at doses higher than 200 mg given once daily. Geometric mean values for the observed R_{ac}, that compares AUC_{tau} for multiple dose administration to AUC_{tau} for single dose administration, ranged from 1.3 to 1.5 for QD dosing and 1.3 to 2.3 for BID dosing. Similar ratios for C_{max} comparison (R_{ac}, C_{max}) ranged from 1.1 to 1.3 for QD dosing and from 1.3 to 2.8 for BID dosing. These results showed that drug concentration accumulation after repeated oral QD or BID administration is less than about 1.5- and 2.3-fold, respectively; at doses up to 200 mg QD, the accumulation was minimal and generally consistent with the prediction from $t_{½}$.

At a single 800 mg dose, the geometric mean C_{max} was similar in Western and Japanese participants. However, geometric mean AUC_{inf} was 26% higher in Western participants than that observed in Japanese participants. Geometric mean C_{max} and AUC_{tau} following multiple dose administration of 200 mg BID was 17% and 56% higher, respectively, in the Western participants than in Japanese participants.

The urinary recovery of abrocitinib was low, with <4% of the dose recovered unchanged in urine across all doses and regimens in all cohorts in Study B7451001.

The BA of a solid dose formulation of abrocitinib relative to a suspension formulation was evaluated in an open-label, single dose, 3 way crossover study in 12 healthy participants under fasting and fed conditions (Study B7451004). Following single oral 400 mg doses under fasted conditions, C_{max} was reached rapidly for the oral suspension (median T_{max} 0.52 hours) and more slowly for the tablet formulation (4×100 mg, median T_{max} 2.0 hours). When the tablet was administered under fed conditions, T_{max} was further delayed with a median value of 4.0 hours. Mean $t_{½}$ was 4.9 hours for the oral suspension fasted, 5.3 hours for the tablet fasted, and 3.2 hours for the tablet under fed conditions. Relative BA of 4×100 mg abrocitinib tablets compared to 400 mg oral suspension under fasted condition was 96.54% and the 90% CI for the ratio (tablet/suspension) of adjusted geometric mean AUC_{inf} values was (90.31%, 103.21%), within the 80% to 125% interval demonstrating equivalence of total exposure. The ratio (90% CI) for C_{max} was 79.48% (62.88%, 100.46%). Administration of 4×100 mg abrocitinib tablets with food did not change AUC_{inf} and appeared to result in slightly lower C_{max} with reduced variability compared to fasted conditions. The ratio (90% CI) of adjusted geometric means for fed/fasted administration was 100.70% (94.42%, 107.40%) for AUC_{inf} and 95.56% (76.22%, 119.82%) for C_{max}. The magnitude of decrease in C_{max} (<5%) was not considered to be clinically important. Therefore, abrocitinib can be administered with or without food. There were no clinically significant changes in ECG findings during the study.

2.2.4.2.2. Population Pharmacokinetics

PK analyses in male and female AD patients and healthy volunteers indicated that systemic exposure (AUC) of abrocitinib in the extremes of body weight (52 kg to 111 kg) was similar (within 20%) to that of a 70 kg individual. The enzymatic activity of CYP enzymes is reduced in patients with atopic dermatitis due to chronic inflammation. Patients with inflammatory disease had approximately 30% higher steady-state abrocitinib exposures compared to healthy volunteers. The observed metabolite/parent ratios of each of the metabolites in AD patients are similar to those observed in healthy subjects. Adolescent patients, including those with lower body weight (down to 25 kg), have similar exposures of abrocitinib compared to adults. There are no clinically relevant differences in exposure for abrocitinib or active moiety in adolescents ≥25 kg compared with adult AD patients. Based on population PK analyses, atopic dermatitis, age, sex, body weight, and race did not have a clinically meaningful effect on exposures of abrocitinib and active moiety.

2.3. Benefit/Risk Assessment

Abrocitinib is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate PK, safety, and tolerability data for further clinical development of abrocitinib. Caffeine, efavirenz, and omeprazole are used as probes of CYP1A2/2B6/2C19, respectively, which PK may be affected by abrocitinib. A study that shows lack of DDI when these substrates are co-administered with abrocitinib improves

confidence in the co-administration of abrocitinib with a wide variety of commonly used drugs.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of abrocitinib may be found in the IB, which is the SRSD for this study.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To estimate effect of multiple dose abrocitinib on the PK of single, oral doses of caffeine, efavirenz and omeprazole in healthy participants.	• AUC_{inf} (if applicable, otherwise AUC_{last}) and of caffeine, efavirenz and omeprazole.
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of abrocitinib when co administered with single doses of caffeine, efavirenz and omeprazole.	• Vital signs, laboratory tests and AEs.
CCI [redacted]	[redacted]
[redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, open-label, multiple dose, single fixed-sequence, 2-period study to evaluate the effect of abrocitinib on the PK of caffeine, efavirenz and omeprazole in healthy adult participants. A total of approximately 13 healthy male and/or female participants will be enrolled in the study to obtain at least 12 evaluable participants who complete the study. Participants who withdraw from the study or are considered non-evaluable may be replaced at the discretion of the sponsor.

Participants will be screened within 28 days of the first dose of study intervention. Participants will have a phone contact 3 days prior to Day 1 dosing (Day -3) in Period 1 as a reminder to abstain from caffeine-containing products. Participants will be admitted to the CRU at least 24 hrs prior to Day 1 dosing (Day -1) in Period 1. Participants will remain in the CRU for a total of 15 days and 14 nights.

In Period 1, all the participants will receive single doses of probe drugs, including caffeine 100 mg, efavirenz 50 mg and omeprazole 10 mg, together on Day 1. The Day 1 of Period 2 begins on the fourth day following the start of Period 1.The predose and up to 24 hours post

dose PK samples will be analyzed for caffeine, efavirenz, and omeprazole; while the 48 and 72 hours post dose PK samples will be analyzed for efavirenz PK only. After 3 days of PK sampling in Period 1, Period 2 will immediately follow with no washout.

In Period 2, participants will receive abrocitinib 200 mg QD on Day 1-10. On Period 2 Day 2, participants will receive single dose of omeprazole 10 mg alone within approximately 5 minutes after administration of a 200 mg dose of abrocitinib in the morning. PK samples for omeprazole concentration measurement will only be collected from predose and up to 8 hours post dose. Participants will receive single doses of the probe drugs (caffeine 100 mg, efavirenz 50 mg and omeprazole 10 mg together) again on Day 8, and omeprazole 10 mg alone on Day 2, within approximately 5 minutes after administration of abrocitinib 200 mg on the morning of the respective day. The predose and up to 24 hours post dose PK samples will be analyzed for caffeine, efavirenz, and omeprazole; while the 48 and 72 hours post dose PK samples will be analyzed for efavirenz PK only.

Participants will have a telephone contact between 28-35 calendar days after the last administration of the investigational product.

The total planned duration of participation, from the Screening visit to the last Follow-up phone call, is approximately up to 11 weeks.

Table 2. Treatment Flow Diagram

Treatment	Period 1		Period 2				
	Day 1	Day 2-3	Day 1	Day 2	Day 3-7	Day 8	Day 9-11
Abrocitinib 200 mg QD			X	X	X	X	X
Caffeine 100 mg SD	X					X	
Efavirenz 50 mg SD	X					X	
Omeprazole 10 mg SD	X			X		X	

4.2. Scientific Rationale for Study Design

Inhibition and induction of the CYP1A2/2B6/2C19 enzymes by abrocitinib were assessed in HLM and human hepatocytes. Abrocitinib was a weak TDI of CYP2C19 and a weak inducer of CYP1A2/2B6/2C19 enzymes. The purpose of the study is to evaluate the effect of abrocitinib on the in vivo PKs of sensitive CYP1A2, 2B6 and 2C19 substrates, caffeine, efavirenz, and omeprazole. The probe drugs used in this study, caffeine, efavirenz, and omeprazole are a subset of the Basel cocktail, which has been validated for simultaneous phenotyping of CYP isoforms[2], and can be used without additional validation.

Multiple dose administration of the investigational drug for a minimum of 7 days is generally recommended to evaluate its induction effect on enzyme activity, as inducers can take several days to exert their effects. While the onset of inhibition effect on CYP enzymes by potential inhibitors is relatively quick. Therefore, caffeine, efavirenz, and omeprazole will be given on Day 8 during the 10 days of abrocitinib QD dosing to assess the potential induction effect of abrocitinib on CYP1A2/2B6, and net effect of TDI and induction on CYP2C19. Omeprazole

will be given on Day 2 to assess the TDI effect of abrocitinib on CYP2C19, with only sparse PK samples to be taken for future exploration using PBPK modeling approach.

Efavirenz has a long $t_{½}$ ranging from 52-76 hours. PK samples collected up to 72 hr may not support $t_{½}$ and AUC_{inf} calculation, therefore, partial AUC_{0-72} hr (AUC_{last}) may be used as the primary endpoint for efavirenz. At a single dose of 50 mg, efavirenz is not expected to induce or inhibit (competitively or mechanism based) any metabolizing system[2].

PK samples collected up to 24 hr is sufficient to capture the full PK profiles of caffeine and omeprazole considering their relatively short half-lives of approximately 5 hr and 1-4 hr, respectively.

CCI [redacted]

4.2.1. Diversity of Study Population

Reasonable attempts will be made to enroll participants with balanced distribution of gender and race to ensure the study population is representative of the patient population that will use abrocitinib in clinical practice.

4.2.2. Choice of Contraception/Barrier Requirements

Human reproductive safety data are not available for abrocitinib, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

CCI [redacted]

4.3. Justification for Dose

Two hundred mg QD oral doses of abrocitinib will be used in this study as it is the highest dose evaluated in the Phase 3 AD program. Both C_{max} and AUC values of abrocitinib increase in proportion to increases in dose following single administrations of up to 400 mg of abrocitinib. Oral doses of abrocitinib as high as 800 mg (single dose), 400 mg QD and 200 mg BID (up to 10 days) have been found to be safe and well-tolerated. Based on the safety data of abrocitinib and prior clinical experience described above, the 200 mg QD for 10 days is expected to pose little risk to healthy adult participants.

Single oral doses of 100 mg caffeine, 50 mg efavirenz, and 10 mg omeprazole will be used in this study as consistent with the validated Basel cocktail. The probe drugs are expected to be generally safe and well tolerated by healthy participants and have no mutual interactions[2].

4.4. End of Study Definition

The end of the study is defined as the date of last scheduled procedure shown in the SoA for the last participant in the study.

A participant is considered to have completed the study if he/she has completed all periods of the study, including the last Follow-up phone call.

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. Participants must be ⩾18 years of age at the time of signing the ICD.

    - 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. Male and female participants who are healthy as determined by medical evaluation including a detailed medical history, complete physical examination, laboratory tests, and cardiovascular tests.

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

Weight:.

4. BMI of 17.5 to 32 kg/m^2; and a total body weight >50 kg (110 lb).

Informed Consent:

5. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the 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 or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

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

3. Participants with moderate to severe GERD symptoms (ie, heartburn and/or regurgitation) during the last 6 months.

4. History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HBsAg, or HCVAb. Hepatitis B vaccination is allowed.

5. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

6. Evidence or history of clinically significant dermatological condition (eg, AD or psoriasis) or visible rash present during physical examination.

7. History of TB (active or latent) or inadequately treated TB infection. Positive QuantiFERON® – TB Gold test.

8. Any history of chronic infections, any history of recurrent infections, any history of latent infections, or any acute infection within 2 weeks of baseline (Day -1).

9. History of disseminated herpes zoster, or disseminated herpes simplex, or recurrent localized dermatomal herpes zoster.

10. Have any malignancies or have a history of malignancies with the exception of adequately treated or excised nonmetastatic basal cell or squamous cell cancer of the skin, or cervical carcinoma *in situ*.

11. History of hypersensitivity, intolerance, or allergic reaction associated to prior exposure to caffeine, omeprazole, efavirenz, and abrocitinib or any of their excipients.

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

    - Suicidal ideation associated with actual intent and a method or plan in the past year: "Yes" answers on items 4 or 5 of the C-SSRS (Section 8.2.7).

    - For participants who had previous history of suicidal behaviors in the past >1 year to 10 years: "Yes" answer (for events that occurred in the past 10 years) to any of the suicidal behavior items of the C-SSRS or any lifetime history of serious or recurrent suicidal behavior, a risk assessment must be performed, and documented, by a qualified MHP to assess whether it is safe for the participant to participate in the trial.

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

    NOTE: For any participant who has significant depression or any suicidal behavior, the participant will not be randomized and should be referred for appropriate evaluation and treatment.

13. Participants, who according to the product label for efavirenz, would be at increased risk if dosed with efavirenz (ie, including but not limited to patients with severe hepatic impairment [Child Pugh Class C]).

14. Participants, who according to the product label for efavirenz, with a history of seizures.

Prior/Concomitant Therapy:

15. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. (Refer to Section 6.8 for additional details).

16. Systemic therapy with any of the medications that are moderate or strong CYP1A2, CYP2B6, or CYP2C19 inhibitors within 28 days or 5 half-lives (whichever is longer) or moderate or strong CYP1A2, CYP2B6, or CYP2C19 inducers within 28 days or 5 half-lives (whichever is longer) prior to the first dose.

17. Herbal supplement, hormonal contraceptives and HRT must be discontinued at least 28 days prior to the first dose of investigational product; Depo-Provera® must be discontinued at least 6 months prior to dosing of investigational product.

18. Participants who are vaccinated with vaccines that have live components (or live attenuated vaccines) within the 6 weeks prior to the first dose of abrocitinib or who are expected to be vaccinated during treatment or during the 6 weeks following discontinuation of abrocitinib.

    NOTE regarding COVID vaccines with authorization or approval for emergency use:

    There is no requirement for washout of COVID vaccines prior to the first dose of abrocitinib if the vaccine is not live attenuated (eg, mRNA, utilizing a viral vector, inactivated virus).

    There is no protocol-specified requirement for the interruption of abrocitinib dosing prior to or after vaccination if the COVID vaccine is not live attenuated.

Prior/Concurrent Clinical Study Experience:

19. 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 study intervention used in this study (whichever is longer).

Diagnostic Assessments:

20. A positive urine drug test.

21. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

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

23. 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 test, if deemed necessary:

    - AST **or** ALT level ≥1.5× ULN;
    - TBili level ≥1.5× ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤1.5× ULN.
    - eGFR <60 mL/min/1.73 m^2 (see Appendix 2 for CKD-EPI formula).
    - In the opinion of the investigator or Pfizer (or designee), have any clinically significant laboratory abnormality that could affect interpretation of study data or the participant's participation in the study.

24. Participants with abnormal complete blood count test results (eg, hemoglobin, platelets, WBCs- including lymphocytes, neutrophils) as assessed by the study specific laboratory, and confirmed by a single repeat test, if deemed necessary.

Other Exclusions:

25. History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces (240 mL) beer, 1 ounce (30 mL) of 40% spirit or 3 ounces (90 mL) of wine).

26. Pregnant female participants; breastfeeding female participants; female participants of childbearing potential who are unwilling or unable to use 1 highly effective method of contraception as outlined in this protocol (see Appendix 4, Section 10.4) for the duration of the study and for at least 28 days after the last dose of study intervention.

27. Participants who routinely consumed more than five 8-ounce cups of coffee (or caffeine equivalent) or greater than 6 servings (1 serving is approximately equivalent to 125 mg of caffeine) of tea, Cola or other caffeinated beverage per day.

28. Consumption of chocolate and chocolate-containing products (eg, hot chocolate, ice cream, cookies, etc) within 48 hours prior to the first dose and during the study.

29. Smokers and/or participants who used nicotine based products within 3 months prior to the first dose of the investigational product.

30. Consumption of charcoal-broiled beef within 7 days prior to the first dose as it is known to induce CYP1A2 enzyme.

31. Consumption of cruciferous vegetables (eg, cauliflower, broccoli, Brussel sprouts, and cabbage) within 7 days prior to the first dose as cruciferous vegetables are known to increase CYP1A2 activity.

32. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.

33. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.

34. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations and 10 hours prior to the collection of the predose PK sample.

- Water is permitted until 1 hour prior to study intervention administration. Water may be consumed without restriction beginning 1 hour after dosing. Noncaffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices–see below) may be consumed with meals and the evening snack.

- Lunch will be provided approximately 4 hours after dosing.

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

- An evening snack may be permitted.

- Participants will refrain from consuming red wine, grapefruit, or grapefruit-related citrus fruits (eg, Seville oranges, pomelos, fruit juices) from 7 days prior to the first dose of study intervention until collection of the final PK blood sample.

- While participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal.

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants will abstain from caffeine-containing products for 48 hours prior to the start of dosing until collection of the final PK sample of each study period.
    - Caffeine–containing products including but not limited to coffee, tea, Cola or other caffeinated beverage (eg, energy drinks), chocolate and chocolate-containing products (eg, hot chocolate, ice cream, cookies, etc), guarana.
- Participants will abstain from alcohol for 24 hours prior (or as specified above for red wine) to admission to the CRU and continue abstaining from alcohol until collection of the final PK sample of each study period. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.
- Participants will abstain from the use of tobacco- or nicotine- containing products for 3 months prior to the start of study intervention in Period 1 and continue abstaining from tobacco- or nicotine-containing products until collection of the final PK sample of Period 2.

5.3.3. Activity

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted;
- In order to standardize the conditions on PK sampling days, participants will be required to refrain from lying down (except when required for BP, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing.

5.3.4. 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 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) considering that their risk for pregnancy may have changed since the last visit. 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.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. Screen failure data are collected and remain as source and are not reported on the CRF.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if prior reason for not meeting the eligibility criteria has been resolved. Rescreening may only occur with Sponsor approval.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

For the purposes of this protocol, study intervention refers to the investigational products, including abrocitinib, caffeine, efavirenz and omeprazole.

6.1. Study Intervention(s) Administered

For this study, the investigational products are abrocitinib (PF-04965842, 200 mg provided as one 200 mg tablet), caffeine (100 mg provided as one 100 mg tablet), efavirenz (50 mg provided as one 50 mg tablet) and omeprazole (10 mg provided as one 10 mg tablet).

Abrocitinib 200 mg tablet will be supplied to the CRU in bulk along with individual dosing containers for unit dosing.

Caffeine 100 mg tablet, efavirenz 50 mg tablet, and omeprazole 10 mg tablet will be supplied locally by the CRU (Upon confirmation that the external CRU will provide comparator agents).

6.1.1. Administration

Period 1: On Day 1, following an overnight fast of at least 10 hours, participants will receive study interventions (100 mg caffeine, 50 mg efavirenz, and 10 mg omeprazole simultaneously) at approximately 08:00 hours (plus or minus 2 hours). Investigator site personnel will administer study intervention with ambient temperature water to a total volume of approximately 240 mL. Participants will swallow the study intervention whole, and will not manipulate or chew the study intervention prior to swallowing.

Period 2: From Day 1 to Day 10, 200 mg abrocitinib will be administered at approximately 08:00 hours (plus or minus 2 hours). On the morning of Day 2, omeprazole will be administered within approximately 5 min after the abrocitinib dose, following an overnight fast of at least 10 hours. On the morning of Day 8, caffeine, efavirenz, and omeprazole will be administered simultaneously within approximately 5 min after the abrocitinib dose, following an overnight fast of at least 10 hours. Investigator site personnel will administer study intervention with ambient temperature water to a total volume of approximately

240 mL. Participants may receive additional ambient temperature water up to 100 mL, if needed.

Participants will swallow the study intervention whole, and will not manipulate or chew the study intervention prior to swallowing.

In order to standardize the conditions on PK sampling days, all participants will be required to refrain from lying down (except when required for BP, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing.

6.2. Preparation, Handling, Storage, and 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.

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 temperatures since previously documented for all site storage locations upon return to business.

3. 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. 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.

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

5. Study interventions should be stored in their original containers.

6. 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), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

7. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. 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.

Upon ID of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

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

Abrocitinib (200 mg provided as one 200 mg tablet), caffeine (100 mg provided as one 100 mg tablet), efavirenz (50 mg provided as one 50 mg tablet) and omeprazole (10 mg provided as one 10 mg tablet) will be prepared in the CRU by 2 operators, 1 of whom is a pharmacist. Prepared doses will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the investigator site's labeling requirements.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

The investigator will assign participant numbers to the participants as they are screened for the study. Pfizer will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the participant will receive the study treatment regimen assigned to the corresponding randomization number.

6.4. Study Intervention Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second qualified member of the study site staff.

6.5. Dose Modification

Dose modification is not allowed in this study.

6.6. Continued Access to Study Intervention After the End of the Study

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

6.7. Treatment of Overdose

For this study, any dose of abrocitinib greater than 800 mg within a 24-hour time period (±12 hours) will be considered an overdose.

Any dose of caffeine greater than 1600 mg within a 24-hour time period (±12 hours) will be considered an overdose[3].

Any dose of efavirenz greater than 600 mg within a 24-hour time period (±12 hours) will be considered an overdose[4].

Any dose of omeprazole greater than 2400 mg within a 24-hour time period (±12 hours) will be considered an overdose[4].

There is no specific treatment for an overdose for abrocitinib. For caffeine, efavirenz or omeprazole, investigators should consider the treatment of overdose as per Scientific Opinion on the Safety of Caffeine[3], or USPIs for efavirenz or omeprazole[4].

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of the study intervention (whichever is longer).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE**.
5. Obtain a blood sample for PK analysis within 4 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

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.

6.8. Concomitant Therapy

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

Systemic therapy with any of the medications that are moderate or strong CYP1A2, CYP2B6, or CYP2C19 inhibitors within 28 days or 5 half-lives (whichever is longer) or moderate or strong CYP1A2, CYP2B6, or CYP2C19 inducers within 28 days or 5 half-lives (whichever is longer), are prohibited prior to the first dose of caffeine.

Females using hormonal contraceptives or taking HRT may be eligible to participate in this study if they are willing to discontinue therapy at least 28 days prior to the first dose of study treatment and remain off hormonal therapy for the duration of the study. Depo Provera® must be discontinued at least 6 months prior to the first dose of study treatment. Note that another approved method of contraception must then be used (Section 10.4.3).

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All participants will be questioned about concomitant treatment at each clinic visit.

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

6.8.1. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with abrocitinib, caffeine, efavirenz or omeprazole; standard medical supportive care must be provided to manage the AEs.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following:

- AE requiring discontinuation in investigator's view;
- Pregnancy;
- Positive COVID-19 test.

If study intervention is permanently discontinued, the participant will not remain in the study for further evaluation. See the SoA for data to be collected at the time of discontinuation of study intervention.

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Refused further study procedures;

- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- At the discretion of the investigator for 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.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) 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.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention 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 study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the

assigned visit schedule and ascertain whether 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.

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.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

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

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

Participants will be screened within 28 days prior to administration of the study intervention to confirm that they meet the study population criteria for the study. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then participants do not require rescreening if the laboratory results obtained prior to first dose administration meet eligibility criteria.

A participant who qualified for this protocol but did not enroll from an earlier cohort/group may be used in a subsequent cohort/group without rescreening, provided laboratory results obtained prior to the first dose administration meet eligibility criteria for this study. C
CI
[redacted]

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.

If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (pulse rate and BP) should be collected prior to the insertion of the catheter.

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

The total blood sampling volume for individual participants in this study is approximately 260 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

To prepare for study participation, participants will be instructed on the information in the Lifestyle Considerations and Concomitant Therapy sections of the protocol.

8.1. Efficacy Assessments

Not applicable.

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 issues.

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems.

A brief physical examination will include, at a minimum, assessments of general appearance, the respiratory and cardiovascular systems, and participant-reported symptoms.

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

Height and weight will also be measured and recorded as per the SoA. For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Participants must remove shoes, bulky layers of clothing, and jackets so that only

light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.3.1 to 8.3.3.

8.2.2. Vital Signs

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

The same properly sized and calibrated BP cuff will be used to measure BP each time. The use of an automated device for measuring BP and pulse rate is acceptable; however, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and pulse rate should be obtained prior to the nominal time of the blood collection.

Additional collection times, or changes to collection times, of BP and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

8.2.2.1. Temperature

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

8.2.3. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10 second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the HR and measures PR, QT, and QTc intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements (Period 1 Day 1, pre-dose). Additional ECG monitoring will occur if a) a postdose QTcF interval is increased by ≥60 msec from the baseline and is >450 msec; or b) an Abs QT value is ≥500 msec for any scheduled ECG. If either of these conditions occurs, then 2 additional ECGs will be collected approximately 2 to 4 minutes apart to confirm the original measurement. If the QTc values from these repeated ECGs remain above the threshold value, then a single ECG must be repeated at least hourly

until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a) a postdose QTcF interval remains ≥60 msec from the baseline and is >450 msec; or b) an Abs QT value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF intervals do not return to less than the criteria listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

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

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

8.2.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

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 calendar 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.

See Appendix 6 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

Participants may undergo random urine drug testing at the discretion of the investigator. Drug testing conducted prior to dosing must be negative for participants to receive study intervention.

8.2.5. COVID-19 specific assessments

Participants will be tested for SARS-COVID-19 infection by PCR prior to being admitted to the clinic for confinement and a subsequent COVID-19 test will be performed after 4 days (i.e. upon completion of 4×24 hours in house), or if they develop COVID-19 like symptoms. Additional testing may be required by local regulations or by the PI.

8.2.6. 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 study intervention. 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 IRBs/ECs or if required by local regulations.

8.2.7. Suicidal Ideation and Behavior Risk Monitoring

The C-SSRS is an interview based rating scale to systematically assess suicidal ideation and suicidal behavior. Versions are available for "lifetime" and "since last evaluation". The "lifetime" evaluation is done at screening, and the "since last evaluation" is done at all other time points.

The C-SSRS should be collected at times specified in the SoA section of this protocol by an appropriately trained CRU staff member. The C-SSRS can also be administered at any time in the study at the discretion of the investigator based on any reasonable concern.

At each suicidality assessments as per SoA, participants felt to have significant suicidal ideation with actual plan and intent or suicidal behavior, must be evaluated by a clinician/MHP skilled in the evaluation of suicidality in the participants by virtue of training or experience (eg, psychiatrist, licensed clinical psychologist) who will determine if it is safe for the participant to participate/continue in the trial. Specific criteria that indicate a need for such an assessment are:

- Suicide ideation associated with actual intent and/or plan in the past year (a "YES" answer to C SSRS questions 4 "some intent to act without specific plan" or 5 "specific plan and intent");
- Previous history of suicide behaviors in the past 10 years (a "YES" answer to any of the suicidal behavior items of the C-SSRS with the behavior occurring in the past 10 years);
- In the investigators judgment a risk assessment or exclusion is warranted.

A written copy of the risk assessment should be included in the participant's clinical record (source documentation).

Other possible suicidality AEs or other clinical observations may, based on the judgment of the investigator, also trigger a risk assessment and require a narrative.

Suicidality AEs or other clinical observations may, based on the judgment of the investigator and clinician/MHP, also trigger a risk assessment and a narrative using information from the C-SSRS, and available information, prior to screening and baseline information, and the clinician/MHP assessment. When there is a positive response to any question on the C-SSRS, the investigator should determine whether an AE has occurred.

At the screening visit, a risk assessment will be done by qualified staff at the CRU to determine whether it is safe for the participant to be enrolled or to continue to participate in the trial.

Participants who respond "YES" to items 4, 5 or to any behavioral question of the C-SSRS at any time after the baseline visit will be assessed by clinician/MHP to determine whether it is safe for the participant to continue in the trial.

Participants who respond "YES" to items 4, 5 or to any behavioral question of the C SSRS on more than one occasion during a trial must have their suicidality managed appropriately by the PI together with clinician/MHP (or the PI alone if the PI is a qualified MHP. Depending on the specifics of the participant as assessed by the PI and/or clinician/MHP, participant may be discontinued from the trial.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

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

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the Investigator or other healthcare providers (clinical signs, test results, etc.).

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 the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

During the active collection period as described in Section 8.3.1, each participant will be questioned about the occurrence of AEs in a nonleading manner.

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 study intervention), through and including a minimum of 28 calendar days after the last administration of the study intervention.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

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

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant permanently discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness 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.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

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 or 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 toward 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, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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

8.3.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure, occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental

exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposure to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, 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. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the 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.

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).

Abnormal pregnancy outcomes are considered SAEs. 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 including 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 study intervention.

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.

8.3.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental EDB is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so 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.

An EDB 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, the SAE is reported together with the EDB.

8.3.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure 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 about the occupational exposure 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 must be maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events (not applicable)

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs (not applicable)

8.3.8. Adverse Events of Special Interest (not applicable)

8.3.8.1. Lack of Efficacy (not applicable)

8.3.9. Medical Device Deficiencies (not applicable)

8.3.10. Medication Errors

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

Exposures to the study intervention under study may occur in CT 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 study intervention;
- 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 within 24 hours.

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 the 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. Pharmacokinetics

If an indwelling catheter is used, approximately 3× the device dead volume of blood will be discarded prior to PK blood collection at each sample collection time point.

Blood samples of approximately 6 mL, to provide a minimum of 2.4 mL plasma, will be collected for measurement of plasma omeprazole, caffeine, and efavirenz concentrations as specified in the SoA. Instructions for the collection, processing, handling, and storage of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

Samples collected for analyses of omeprazole, caffeine, and efavirenz plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolites 5-hydroxy omeprazole, paraxanthine, and 8-hydroxy efavirenz concentrations, metabolite identification and/or evaluation of the bioanalytical method, [redacted]

Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

PK samples will be analyzed using a validated analytical method in compliance with applicable SOPs. Potential metabolites may be analyzed with either validated [redacted] methods.

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.

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

CCI [redacted]

8.7. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.8. Health Economics

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

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 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. Statistical Hypotheses

No formal inferential statistics will be applied to the data.

9.2. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Enrolled/Randomly assigned to study intervention	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.
PK Concentration	The PK concentration population is defined as all enrolled participants who received at least 1 dose of investigational product and in whom at least 1 plasma concentration value is reported.
PK Parameter	The PK parameter analysis population is defined as all participants who received at least 1 dose of investigational product and have at least 1 of the PK parameters of interest in at least 1 treatment period.
Safety Analysis Set	All participants randomly assigned to investigational product and who take at least 1 dose of investigational product. Participants will be analyzed according to the product they actually received.

9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.3.1. Pharmacokinetic Analysis

9.3.1.1. Analysis Population

The PK concentration population is defined as all participants randomized and treated who have at least 1 concentration in at least 1 treatment period.

The PK parameter analysis population is defined as all participants randomized and treated who have at least 1 of the PK parameters of primary interest in at least 1 treatment period.

CCI [redacted]

9.3.1.2. Derivation of Pharmacokinetic Parameters

PK parameters will be derived from the plasma concentration time profiles as shown in Table 3.

Table 3. Plasma Pharmacokinetic Parameter Definitions

Parameter	Definition	Method of Determination
AUC_{last}	area under the concentration-time curve from time 0 to time of the last measureable concentration	Linear/Log trapezoidal rule
AUC_{inf}	area under the concentration-time curve from time 0 to infinity	$AUC_{last} + (C_{last}^*/k_{el})$, where C_{last}^* is the predicted plasma concentration at the last quantifiable time point estimated from the loglinear regression analysis, and k_{el} is the terminal phase rate constant calculated by a linear regression through at least 3 data points in the terminal phase of the loglinear concentration time curve
CC [redacted]	[redacted]	[redacted]
CC I [redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted]
G C I [redacted]	[redacted]	[redacted]

Natural log-transformed parameters (AUC_{inf}, AUC_{last} [redacted]) will be analyzed using a mixed effect model with treatment as a fixed effect and subject as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CI for the ratios. The Test and Reference treatments to estimate the treatment difference for each of the study objectives are as follows:

- Objective 1: caffeine 100 mg (Period 1, Day 1) will be the Reference treatment; abrocitinib 200 mg + caffeine 100 mg (Period 2, Day 8) will be the Test treatment.
- Objective 2: efavirenz 50 mg (Period 1, Day 1) will be the Reference treatment; abrocitinib 200 mg + efavirenz 50 mg (Period 2, Day 8) will be the Test treatment.
- Objective 3: omeprazole 10 mg (Period 1, Day 1) will be the Reference treatment; abrocitinib 200 mg + omeprazole 10 mg (Period 2, Day 8) will be the Test treatment.

Residuals from the model will be examined for normality and the presence of outliers via visual inspection of plots of residuals vs predicted values and normal probability plots of residuals but these will not be included in the CSR. If there are major deviations from normality or outliers, then the effect of these on the conclusions will be investigated through alternative transformations and/or analyses excluding outliers. Justification for any alternative to the planned analysis will be given in the report of the study.

9.3.2. Other Safety Analyses

All safety analyses will be performed on the safety population.

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

Medical history and physical examination and neurological examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

[redacted]

9.4. Interim Analyses

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, and/or supporting clinical development.

9.5. Sample Size Determination

A sample size of 12 participants will provide 90% CIs for the difference between treatments of ±0.1099, ±0.2029 and ±0.2114 on the natural log scale for AUC_{inf} in the assessment of caffeine, efavirenz, and omeprazole, respectively, with 80% coverage probability. The width of 90% CIs for different estimated effects is presented in Table 4.

Table 4. Width of 90% CIs for Different Estimated Effects of Test/Reference Ratio

Reference	Estimated Effect (100×Test/Reference) (%)	AUC_{inf}	
		90% CI (%)	CI Width (%)
Caffeine	80	(71.67, 89.29)	17.62
	90	(80.63, 100.46)	19.83
	100	(89.59, 111.62)	22.03
	110	(98.55, 122.78)	24.23
	120	(107.51, 133.94)	26.44
Efavirenz	80	(65.31, 98.00)	32.69
	90	(73.47, 110.25)	36.78
	100	(81.63, 122.50)	40.87
	110	(89.80, 134.75)	44.95
	120	(97.96, 147.00)	49.04
Omeprazole	80	(64.76, 98.83)	34.08
	90	(72.85, 111.19)	38.34
	100	(80.95, 123.54)	42.59
	110	(89.04, 135.89)	46.85
	120	(97.13, 148.25)	51.13

These estimates are based on the assumption that within-participant standard deviations are 0.13, 0.24 and 0.25 for $lnAUC_{inf}$ of caffeine, efavirenz, and omeprazole, respectively, as obtained from previous Pfizer studies in healthy participants.

Participants who fail to complete the study may be replaced at the discretion of the sponsor.

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 CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, 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.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), European MDR 2017/745 for clinical device research (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 study intervention, 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 the ICH GCP guidelines that the investigator becomes aware of.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection 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 on which 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

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 will 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 participants 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 and medical record ID. 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. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use a DMC.

10.1.6. 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 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 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 CT 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. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts CT results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

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 corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the EU Policy 0070, the proactive publication of clinical data to the 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 contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 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.

10.1.7. 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.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

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, including definition of study critical data items and processes (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, virtual, or on-site monitoring), are provided in the data management plan [and monitoring plan] maintained and utilized by the sponsor or designee.

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

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.

10.1.8. 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 eCRF that are 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 and its origin can be found in the clinical monitoring plan, which is maintained by the sponsor.

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor.

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

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 guidelines, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

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 sponsor or designee/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 the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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.

10.1.10. 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 the 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.

10.1.11. 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 STOD.

To facilitate access to appropriately qualified medical personnel for study-related medical questions or problems, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study ID number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the investigator, site staff, and study team. The ECC is to be used by healthcare professionals not involved in the research study only, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number should only be used when the investigator and site staff cannot be reached. The Pfizer Call Center number is not intended for use by the participant directly; if a participant calls that number directly, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The safety laboratory tests listed in Table 5 will be performed at times defined in the SoA 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.

The eGFR will be calculated using the following equation developed by the CKD-EPI which utilizes SCr:

CKD-EPI

If female and SCr is ≤0.7 mg/dL:

$$GFR\ (mL/min/1.73\ m^2) = 144 \times (SCr/0.7)^{-0.329} \times 0.993^{age}\ (\times 1.159, \text{if Black}).$$

If female and SCr is >0.7 mg/dL:

$$GFR\ (mL/min/1.73\ m^2) = 144 \times (SCr/0.7)^{-1.209} \times 0.993^{age}\ (\times 1.159, \text{if Black}).$$

If male and SCr is ≤0.9 mg/dL:

$$GFR\ (mL/min/1.73\ m^2) = 141 \times (SCr/0.9)^{-0.411} \times 0.993^{age}\ (\times 1.159, \text{if Black}).$$

If male and SCr is >0.9 mg/dL:

$$GFR\ (mL/min/1.73\ m^2) = 141 \times (SCr/0.9)^{-1.209} \times 0.993^{age}\ (\times 1.159, \text{if Black}).$$

Table 5. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN/urea and creatinine Cystatin C Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT TBili Alkaline phosphatase Uric acid Albumin Total protein eGFR based on the CKD-EPI equation	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	• COVID-19 testing • Urine drug screening[b] • Pregnancy test[c] <u>At screening only:</u> • FSH[d] • HBsAg • HBcAb • HBsAb[e] • HCVAb • HIV • QuantiFERON®-TB Gold Test[f]
	Additional Tests (Needed for Hy's Law)		

Table 5. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
	AST, ALT (repeat) TBili (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin CK GGT PT/INR Total bile acids Acetaminophen drug and/or protein adduct levels		

a. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
b. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site specific).
c. Pregnancy test for female participants of childbearing potential.
d. For confirmation of postmenopausal status only (only females who are amenorrheic for at least 12 consecutive months).
e. HBsAb tested as reflex test only in participants who are HBsAg negative, but are HBcAb positive.
f. Complete at screening. Previous testing for QuantiFERON®-TB Gold Test will be accepted if completed within 12 weeks prior to baseline. Otherwise should be completed at screening and results available prior to Day 1.

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.

Any remaining serum from samples collected for clinical safety laboratory measurements at baseline and at all times after dose administration may be retained and stored for the duration of the study. CCI [redacted]

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. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms;
 	
  • Requires additional diagnostic testing or medical/surgical intervention;
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition.
 	
• New condition 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 DDI.
 	
• 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 or SAE unless it is an intentional overdose taken with possible

suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that 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 an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:

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 admitted (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 or significant 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), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious.

The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that 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 During the Active Collection Period

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the CT SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs;

(2) nonserious AEs; and (3) exposure to the study intervention 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 study intervention under study during pregnancy or breastfeeding	All AEs/SAEs associated with EDP or breastfeeding **Note:** Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF.	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE). **
Environmental or occupational exposure to the product under study to a non-participant (not involving EDP or EDB).	None. Exposure to a study non-participant is not collected on the CRF.	The exposure (whether or not there is an associated AE or SAE) must be reported.***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using CT SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the CT SAE Report Form.

** **EDB** is reported to Pfizer Safety using the CT SAE Report Form which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or Occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form.

- When an AE or 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 or 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 or 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 or 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: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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 or SAE. The investigator will use clinical judgment to determine the relationship.

- 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.

- 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 IB and/or product information, for marketed products, in his/her assessment.

- For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or 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 study intervention caused the event, then the event will be handled as "related to study intervention" 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 providers.

- 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 submitted documents.
- 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 DCT.
- If the electronic system is unavailable, then the site will use the paper SAE DCT (see next section) 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 DCT 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 DCT 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 and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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

According to the efavirenz or omeprazole USPIs, there is no requirement for male contraceptive use during treatment

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), 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 reproductive safety risk of the study intervention(s). If a highly effective method that is user dependent is chosen, a second effective method of contraception, as described below, must also be used. 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

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

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

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

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;

- Documented bilateral salpingectomy;
- Documented bilateral oophorectomy.

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

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

2. Postmenopausal female.

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:
  - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.
  - For Women using HRT, FSH should be measured after an appropriate washout of HRT (at least 14 days after the last dose of HRT). HRT must be discontinued at least 28 days before first dose of investigational product during the study.
  - Females whose menopausal status is in doubt will be required to use one of the allowed non-hormonal highly effective contraception methods.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in CTs.

Highly Effective Methods That Are User Dependent

1. Non-hormonal IUD.
2. Bilateral tubal occlusion (eg, bilateral tubal ligation).
3. Vasectomized partner.

- A vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective

method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

4. 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.

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 DILI. Participants who experience a transaminase elevation above 3× ULN should be monitored more frequently to determine if they are "adaptors" or are "susceptible".

In the majority of DILI cases, elevations in AST and/or ALT precede 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 Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/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/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or 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, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol 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 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 AEs

- Marked sinus bradycardia (rate <40 bpm) lasting minutes.
- New PR interval prolongation >280 msec.
- New prolongation of QTcF to >480 msec (Abs) 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 PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.

ECG Findings That <u>May</u> Qualify as SAEs

- QTcF prolongation >500 msec.
- New ST-T changes suggestive of myocardial ischemia.
- New-onset LBBB (QRS >120 msec).
- New-onset right bundle branch block (QRS >120 msec).
- Symptomatic bradycardia.
- Asystole:
  - In awake, symptom-free participants 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 participants 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 (HR <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >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 SAEs

- 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: Abbreviations

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

Abbreviation	Term
Abs	absolute
AD	atopic dermatitis
ADL	activities of daily living
AE	adverse event
AIA	adjuvant-induced arthritis
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-72}	area under the concentration-time curve from time 0 to 72 hours.
AUC_{24}	area under the concentration-time curve from time 0 to 24 hours
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
AUC_{last}	area under the concentration-time curve from time 0 to time of the last measureable concentration
AUC_{tau}	area under the concentration-time curve at steady state over the dosing interval τ
AV	atrioventricular
BA	bioavailability
CCI	[redacted]
BCRP	breast cancer resistance protein
BID	twice a day
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	apparent clearance of drug from eg, plasma
C_{last}	last quantifiable concentration
C_{max}	maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report

Abbreviation	Term
C-SSRS	the Columbia Suicide Severity Rating Scale
CT	clinical trial
CYP	cytochrome P450
DCT	data collection tool
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FOB	functional observational battery
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
hERG	human ether-à-go-go related gene
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC_{50}	50% inhibitive concentration
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identity
IFN-α	interferon-alpha
IFN-γ	interferon-gamma
IL	interleukin

Abbreviation	Term
IND	Investigational New Drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IUD	Intrauterine device
IV	intravenous
JAK	Janus Kinase
KDR	kinase insert domain receptor
k_{el}	elimination rate constant
LBBB	left bundle branch block
LFT	liver function test
MAO-A	Monoamine oxidase A
MATE	multidrug and toxin extrusion protein
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDR	medical device regulation
MHP	mental health professional
mRNA	messenger ribonucleic acid
msec	millisecond
N/A	not applicable
NOAEL	no observed adverse effect level
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
PBMC	Peripheral blood mononuclear cell
PCR	polymerase chain reaction
P-gp	p-glycoprotein
PGx	pharmacogenomic(s)
pH	negative logarithm of hydrogen ion concentration
PI	primary investigator
PK	pharmacokinetic(s)
PT	prothrombin time
PVC	premature ventricular contraction/complex
QD	once daily
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
qual	qualitative
R_{ac}	accumulation ratio based on AUC (observed)
RBC	red blood cell

Abbreviation	Term
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS	severe acute respiratory syndrome
SCr	serum creatinine
SoA	schedule of activities
SOC	System Organ Class
SOP	standard operating procedure
SRSD	single reference safety document
STAT	signal transducer and activator of transcription
STOD	Study Team on Demand
SULT	sulfotransferase
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	terminal phase half-life
TB	tuberculosis
TBili	total bilirubin
TDI	time-dependent inhibition
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
T_{max}	time to reach C_{max}
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
US	United States
VEGFR2	vascular endothelial growth factor receptor 2
V_z/F	apparent volume of distribution for extravascular dosing
WBC	white blood cell
WOCBP	woman/women of childbearing potential

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