AN OPEN LABEL, PHASE 1, TWO-ARM STUDY TO ASSESS TARGET OCCUPANCY AND FUNCTIONAL INHIBITION OF JAK3 AND TEC KINASES BY SINGLE DOSES OF RITLECITINIB IN HEALTHY ADULT PARTICIPANTS

Study Intervention Number:	PF-06651600
Study Intervention Name:	Ritlecitinib
US IND Number:	CCI [redacted]
EudraCT Number:	N/A
ClinicalTrials.gov ID:	N/A
Protocol Number:	B7981045
Phase:	1

Brief Title: A Phase 1 target occupancy study with ritlecitinib.

Document History

Document	Version Date
Amendment 2	10 November 2021
Amendment 1	01 October 2021
Original protocol	12 August 2021

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any global protocol administrative clarification letter.

Protocol Amendment Summary of Changes Table

Amendment 2 (10-November-2021)

Overall Rationale for the Amendment: This amendment is to clarify acceptable forms of contraception for women of child bearing potential.

Section # and Name	Description of Change	Brief Rationale
10.4.2. Female Participant Reproductive Inclusion Criteria	1. Removal of "with low user dependency".	To maintain consistency with Section 10.4.4.
10.4.4 Contraception Methods	1. Removal of bullet points 6 and 7: "Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation. a. Oral; b. Intravaginal; c. Transdermal. Progestogen only hormone contraception associated with inhibition of ovulation. a. Oral; b. Injectable".	To provide appropriate contraception guidance for study participants

Section # and Name	Description of Change	Brief Rationale
	2. Removal of "One of the following effective barrier methods must be used in addition to the highly effective methods listed above that are user dependent: a. Male or female condom with or without spermicide; b. Cervical cap, diaphragm, or sponge with spermicide; c. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)".	

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1. PROTOCOL SUMMARY

1.1. Synopsis

An open label, Phase 1, two-arm study to assess target occupancy and functional inhibition of JAK3 and TEC kinases by single doses of ritlecitinib in healthy adult participants

Brief Title:

A Phase 1 target occupancy study with ritlecitinib.

Rationale

This study aims to assess the target coverage/TO by ritlecitinib of two distinct families of kinases that are irreversibly bound (JAK3 and TEC kinases). In addition to TO, the study will include an assessment of the effect of ritlecitinib on pathways that functionally depend on either JAK3 or TEC kinases. Together these results will enable a more complete assessment of the relative degree of pathway coverage over a broad range of exposures and over a length of time that allows for recycling/production of new target (ie JAK3 and TEC family kinases).

Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
• To characterize the TO of JAK3 and TEC kinases in peripheral blood mononuclear cells (PBMCs) after single oral dose of ritlecitinib	• Percent TO for JAK3 and TEC kinases (BTK, ITK, RLK, TEC and BMX)
Secondary:	**Secondary:**
• To evaluate the plasma exposure of ritlecitinib over 48 hours after single oral dose administration	• Ritlecitinib plasma PK parameters • C_{max}, T_{max}, C_{last}, C_{av}, AUC_{last} and, AUC_{24}
• To evaluate the safety and tolerability of an oral dose of ritlecitinib when administered alone and in healthy adult participants	• Assessment of TEAEs, clinical laboratory tests, and vital signs
Tertiary:	**Tertiary:**
• To characterize the relationship between TO in PBMCs and plasma ritlecitinib exposure over 48 hours after single oral dose	• Maximal inhibition (occupancy) by ritlecitinib (TO_{max}) • Ritlecitinib plasma concentrations at 50% TO_{max} (IC_{50})

CCI [redacted]

Overall Design

Brief Summary

This is a Phase 1, open label, parallel group, two-arm study to assess target occupancy and functional inhibition of JAK3 and TEC kinases by single doses of ritlecitinib in healthy adult participants.

Ritlecitinib is not expected to provide any clinical benefit to healthy participants. This study is designed to evaluate JAK3 and TEC kinase inhibition data for further clinical development.

Number of Participants

Approximately 16 participants will be enrolled to study intervention.

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

Single doses of 50 mg and 200 mg are being used in the study which are expected to encompass concentrations observed in patient populations at clinically relevant doses.

Participants will be enrolled to receive either 50 mg or 200 mg single dose of ritlecitinib on Day 1. Blood samples to assess ritlecitinib PK, target occupancy and functional assays will be collected over 48 hours. Participants will remain in the CRU until Day 3 when they will be discharged after completion of study activities.

No dose changes/adjustments including flexible dosing; dose reductions, interruptions, or tapering is allowed as per study protocol.

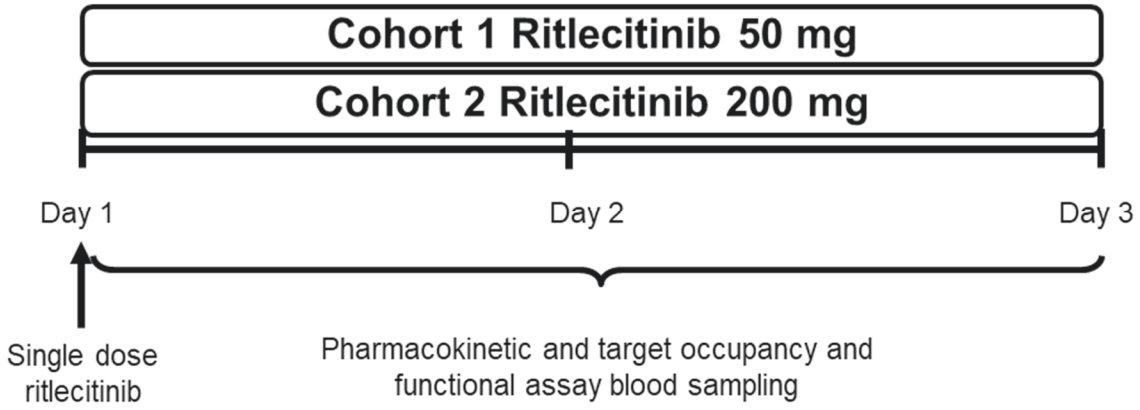
Data Monitoring Committee or Other Independent Oversight Committee: No

Statistical Methods

Percent TO [redacted] will be assessed graphically and summarized by nominal timepoints using descriptive statistics. In addition, relationship between TO and plasma exposure of ritlecitinib will be assessed graphically and suitable exposure-response population models will be explored to quantify the relationship.

1.2. Schema

Figure 1. Study Schema



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.

Table 1. Schedule of Activities for Study

Visit Identifier	Screening					ET	Follow-up[l]
Days Relative to Day 1[a]	**D -28 to D -2**	**D -1**	**D 1**	**D 2**	**D 3**		
Informed consent	X						
CRU confinement		X	→	→	X		
Inclusion/exclusion criteria	X	X					
Medical/medication history	X	X					
Physical examination[b]	X	X					
Safety laboratory	X	X			X	X	
Demography (including height & weight)	X						
Contraception check	X	X			X	X	X
Pregnancy test (WOCBP only)	X	X			X	X	
Serum FSH (postmenopausal women only)[c]	X						
Urine drug testing	X	X					
Vital signs (supine BP and pulse rate)	X		X[d]		X	X	
12 Lead ECG (single)	X		X[d]		X	X	
HIV, HBsAg, HBcAb, HCVAb screen[e]	X						
QFT-G	X						
COVID-19 questionnaire[f]	X	X					
COVID-19 testing[g]	X	X					
COVID-19 check temperature[h]	X	→	→	→	X		
Retained Research Samples for Genetics (Prep D1)[i]			X				
Ritlecitinib dosing[j]			X				
Ritlecitinib PK blood sample[k]			X	X	X	X	
Functional assay blood sampling[k]			X	X	X		

Table 1. Schedule of Activities for Study

Visit Identifier	Screening					ET	Follow-up[l]
Days Relative to Day 1[a]	**D -28 to D -2**	**D -1**	**D 1**	**D 2**	**D 3**		
Target occupancy blood sampling[k]			X	X	X		
CRU discharge					X		
Prior/Concomitant medication assessment	X	→	→	→	→	X	X
Serious and nonserious AE monitoring	X	→	→	→	→	X	X

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

b. Complete physical exam could be done at screening or admission on Day -1. Brief physical exam to be done only in case of finding at previous exam or new/open AE if applicable, at the discretion of the investigator.

c. Any female who has been amenorrheic for at least 12 consecutive months.

d. Collect before drug administration.

e. All participants will undergo screening for Hepatitis B, Hepatitis C and HIV for eligibility. Please refer to Section 5.2 for testing algorithm, reflex testing, and full eligibility criteria.

f. Check exposure to positive participant, residence or travel in area of high incidence and COVID-19 related signs and symptoms.

g. 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 symptom(s).

h. To be done twice daily during residence.

i. Prep D1 Retained Research Samples for Genetics: If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.

j. Participants will be dosed with ritlecitinib following an overnight fast of at least 10 hours at approximately 08:00±2 hours.

k. Refer to Table 2 for details of ritlecitinib dosing, ritlecitinib PK sampling, functional assay blood sampling and target occupancy assay blood sampling.

l. Participants will have a telephone contact at least 28 calendar days, and up to 35 calendar days after the last administration of the investigational product(s). At the discretion of the investigator, telephone contact may be substituted with an on-site visit in case of additional follow-up of open AEs or clinically significant laboratory findings.

Table 2. Table of Blood Sampling for Study Drug, Functional Assay and Target Occupancy

Study Day	**1**						**2**	**3**
Hours Before/After Dose	**-1[a]**	**0[a]**	**1**	**2**	**4**	**8**	**24**	**48**
Ritlecitinib dosing		X						
Ritlecitinib PK blood sampling		X	X	X	X	X	X	X
CCI [redacted]								
Target occupancy blood sampling	X	X	X	X	X	X	X	X

a. Predose samples.

2. INTRODUCTION

Ritlecitinib (previously known as PF-06651600) is a potent, covalent, and irreversible inhibitor of JAK3 with high selectivity over the other three JAK isoforms (JAK1, JAK2, and TYK2. Ritlecitinib also inhibits irreversibly the TEC family kinases BTK, BMX, ITK, RLK, and TEC) with selectivity over the broader human kinome. Ritlecitinib is being developed for the treatment of UC, CD, AA, RA, and vitiligo.

2.1. Study Rationale

Inhibition of JAK3 by ritlecitinib is expected to modulate γ-common chain cytokine pathways, such as IL-7, IL-9, IL-15, and IL-21, but expected to spare inhibition of other JAK-dependent pathways that do not utilize JAK3, including IL-6 signaling and key immuno-suppressive cytokines, such as IL-10, IL-27 and IL-35.[1] Selective JAK3 targeting may reduce adverse effects from other JAK pathways, including cytopenia's (JAK2-dependent), cardiovascular events, malignancies, and severe infections. Inhibition of TEC kinases by ritlecitinib is expected to modulate T cell and B cell development and function (TEC kinases are activated downstream of the TCR and BCR). These effects by ritlecitinib on TCR signaling have been shown to inhibit the cytotoxic function of CD8+T cells and NK cells.[2] There is limited information on the degree of target occupancy by Ritlecitinib on JAK3 and TEC kinases (ie, irreversible kinase binding) in humans, and how TO and target turnover of both JAK3 and TEC kinases a) is regulated by drug half-life, and b) how TO translates into functional effects on specific cell types and pathways.[3]

TO of JAK3 and the five TEC kinases by ritlecitinib has been demonstrated in vivo in NOD-scid IL2rγ-null mice engrafted with human PBMCs which expresses JAK3 and TEC kinases.[2] Despite the large variation in occupancy measurements likely due to differing levels of human PBMC engraftment and the small number of mice (n=3) per time point, approximately 100% occupancy of JAK3 and most of the TEC kinases, except RLK, was observed in the spleen samples from early time points (0.25 to 5 h). A slower recovery of unbound BTK was seen compared to JAK3 and ITK due to relatively longer half-life of BTK (12-24 hours vs. 2-3 hours for JAK3/ITK). Since the PK profile of ritlecitinib is characterized by rapid absorption and rapid elimination half-life, it is important to study the relationship between TO of JAK3 and the TEC kinase family and the functional consequences of their inhibition over time by ritlecitinib in healthy participants to provide insights in assessing the impact in patients with inflammatory and autoimmune diseases. Based on the predicted PK for ritlecitinib, along with the need to assess target occupancy (and functional inhibition) in a predefined specimen collection window, at least 2 doses would be required to capture expected concentrations in patients at clinically relevant doses and also to better understand the expected hysteresis in exposure and response.

2.2. Background

2.2.1. Nonclinical Pharmacology

Ritlecitinib is a potent, covalent, and irreversible inhibitor of JAK3 with high selectivity over the other 3 JAK isoforms (JAK1, JAK2, and TYK2). Ritlecitinib also inhibits irreversibly the TEC kinase family (BTK, BMX, ITK, TEC and RLK/TXK), with high selectivity over the broader kinome. In hWB, ritlecitinib potently inhibits signaling of the common- γ chain receptors for IL-2, IL-4, IL-7, IL-15, and IL-21 but does not inhibit signaling of cytokines that are JAK3 independent such as IL-10, IFNα, IL-6, IL-27, IL-12 and IL-23 or EPO signaling in CD 34+ progenitor cells. In addition, ritlecitinib also inhibits the cytotoxic function of CD8+T cells and NK cells.

Further information is available in the current version of the ritlecitinib IB.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

In vitro and in vivo metabolite profiling indicated that glutathione related conjugation is the primary clearance mechanism for ritlecitinib with minor CYP450-mediated oxidation.

Regarding enzymatic DDI, ritlecitinib showed a low risk of in vitro interaction due to reversible inhibition of the major CYP450, UGT, GST, and SULT enzymes at a maximum clinical daily dose of 200 mg (unbound C_{max} 4.8 μM). However, ritlecitinib showed in vitro evidence of DDI of CYP3A and CYP1A2, and there was in vitro induction of CYP3A4 and CYP2B6 mRNA levels at 50 to 100 μM, while no CYP1A2 induction was noted. Clinically, ritlecitinib showed a moderate impact on midazolam (C_{max} ratio 1.81; AUC_{inf} ratio 2.69) and no impact on effavirez (CYP2B6) exposure. Therefore, the predominant ritlecitinib effect on CYP3A4 is inhibition, with no evidence of induction for either CYP3A4 or CYP2B6.

Regarding transporter DDI, ritlecitinib is not a substrate for OATP1B1 or OATP1B3. However, ritlecitinib showed an in vitro risk of DDI with BCRP, OATP1B1, OCT2, OAT1, OAT3, OCT1, MATE1, and MATE2K. In a clinical DDI study, a minor decrease in the Cmax ratio (0.74) of rosuvastatin (BCRP) but no effect on its AUC_{inf} (OATP1B1) or renal clearance (OAT3) were observed with co-administration of ritlectinib. In addition, there were no significant changes in creatinine clearance (OCT2/MATE1/2K) from baseline with multiple doses up to 800 mg of ritlecitinib. These results suggest that there was no clinically significant inhibition of these transporters in vivo.

Further information is available in the current version of the ritlecitinib IB.

2.2.3. Nonclinical Safety

Ritlecitinib was administered QD for up to 6 months in rats and 9 months in dogs (two 9-month dog studies were conducted). The NOAEL in the 6-month rat and second 9-month dog studies were 200 and 10 mg/kg/day (unbound AUC values of 53,700 and 7940 ng•h/mL), respectively. Based on the results of the nonclinical studies, target organs identified following ritlecitinib administration include CNS/PNS in dogs, the immune and hematolymphopoietic systems (thymus, spleen, lymph nodes, bone marrow, circulating

lymphocytes, and red blood cells) and adrenal gland in rats and dogs, kidney in rats, and the GI system in dogs. Functional effects on the cardiovascular system (heart rate and BP) were also observed in dogs. Effects on bone marrow and the immune and hematolymphopoietic systems were consistent with the known pharmacological activity of JAK3 and/or TEC kinase inhibition.

In a second GLP compliant 9 month toxicity study in dogs, adverse effects following administration of ritlecitinib consisted of decreased lymphoid cellularity in animals administered ≥20 mg/kg/day leading to over-immunosuppression based on evidence of skin infection (Demodex spp, papillomavirus, and interdigital cysts); axonal dystrophy in the CNS and PNS in animals administered ≥20 mg/kg/day and in the autonomic nerves of the adrenal gland in animals administered 20 (20 QD) mg/kg/day; and auditory threshold and waveform deficits in the BAEP associated with the axonal dystrophy at 40 mg/kg/day.

Ritlecitinib was not genotoxic in the microbial reverse mutation assay or the in vivo rat micronucleus assay but was positive in an in vitro micronucleus assay in human lymphoblastoid TK6 cells. Based on a follow-up chromosome aberration test that was negative and a flow cytometric aneuploidy assessment that demonstrated an increase in hypodiploidy, hyperdiploidy, and polyploidy, an aneugenic mechanism of action was determined. Ritlecitinib did not induce micronuclei in polychromatic reticulocytes when administered to rats for 4 days as part of the 8-week pivotal study. Nonpivotal dose range-finding and pivotal EFD studies in rats and rabbits were conducted. In the pivotal EFD study in rats, fetal skeletal malformations and variations, and decreased fetal weights were observed; in the pivotal EFD study in rabbits, fetal skeletal and visceral malformations, skeletal variations, and decreased fetal weights were observed. Ritlecitinib did not produce a positive response in the mouse allergy model, suggesting low likelihood of hypersensitivity reactions. There was no evidence of cutaneous or ocular phototoxicity after oral administration of ritlecitinib to rats for 3 days at doses up to 200 mg/kg/day.

Further information is available in the current version of the ritlecitinib IB.

2.2.4. Clinical Overview

Ritlecitinib has been evaluated in healthy participants in a FIH B7981001 study, in a bioavailability (BA) B7981003 study which compared the relative BA of solution versus tablet, and a PK study in healthy Japanese participants (B7981008). Ritlecitinib has also been evaluated in participants in a PK DDI study to evaluate the potential steady state DDI in healthy adult participants between IRAK4 (PF-06650833) and ritlecitinib (B7981028). It has also been evaluated in participants with moderate to severe RA in B7981006 and in patients with moderate to severe alopecia areata (B7931005). There are ongoing studies in participants with moderate to severe alopecia areata (B7981015), active non-segmental vitiligo (B7981019), moderate to severe active ulcerative colitis (B7981005), and moderate to severe active Crohn's disease (B7981007).

Studies in healthy participants

The FIH study (B7981001) was a Phase 1, randomized, double-blind, third-party open, placebo controlled, single and multiple dose escalation, parallel group study in healthy adult participants. During the single dose period, participants received doses of 5, 20, 50, 100, 200, 400, or 800 mg of ritlecitinib in a dose escalation format. Participants returned for the multiple dose period to receive doses of 50, 200, or 400 mg QD or 100 or 200 mg BID for 14 days.

B7981008 was a Phase 1, randomized, double blind, third-party open, placebo-controlled study to evaluate the safety, tolerability, PK and PD after multiple oral doses of ritlecitinib in healthy Japanese adult participants. Six participants were randomized, with 2 participants receiving placebo and 4 participants receiving ritlecitinib 200 mg QD, respectively.

B7981003 was a Phase 1, open label, single-dose 3-way crossover study to evaluate the relative bioavailability of a solid dose formulation of ritlecitinib under fasting conditions and the effect of a high fat meal on the bioavailability of the solid dosage formulation of PF-06651600 in healthy participants. A total of 14 participants were randomized to study treatment.

In all the above studies, ritlecitinib was found to be well tolerated and to have an acceptable safety profile.

Summary of Clinical PK

The PK profile of ritlecitinib is characterized by rapid absorption median (T_{max} ranging from ≤0.75 – 1.5 hour), rapid elimination (t½ of ~2 hours) and are approximately dose proportional. Steady state generally appears to be reached by Day 4 for the QD regimens and Day 6 for the BID regimens based on similar median trough (predose) ritlecitinib beyond Day 6. Ritlecitinib has been evaluated at single oral doses ranging from 5 mg to 800 mg and multiple oral doses ranging from 50 mg to 400 mg QD and at 100 mg and 200 mg BID for 14 days. The clearance mechanisms for ritlecitinib in humans appear to be primarily by metabolism. Less than 10% of ritlecitinib is excreted unchanged in the urine.

In vitro and in vivo metabolite profiling suggested that the primary clearance mechanisms for ritlecitinib were both CYP450 mediated oxidation and glutathione related conjugation. Biliary excretion of ritlecitinib was limited in the rat and renal elimination was limited in humans. Reaction phenotyping in recombinant enzyme systems identified CYP3A4 as the predominant CYP450 isoform responsible for the metabolism of ritlecitinib, with minor contributions from CYP2C19 and CYP3A5.

CCI [redacted]

Further information is available in the current version of the ritlecitinib IB.

Phase 2a Study in RA

The completed Phase 2a study B7981006 was an 8-week randomized, double blind, placebo controlled, parallel group, multi-center study in participants with moderate to severe active RA with an inadequate response to methotrexate. A total of 70 participants were randomized to study treatment; 28 participants received placebo and 42 participants received ritlecitinib on background of methotrexate. Ritlecitinib was determined to be generally safe and well tolerated in this study. There were no deaths or SAEs. TEAEs were numerically higher in participants receiving ritlecitinib compared to those receiving placebo. The TEAEs reported in more than 5% (1 in 20) participants with RA receiving ritlecitinib were influenza and lymphopenia. Most of the AEs were mild in severity. There was 1 mild case of herpes simplex in the ritlecitinib group that was considered to be treatment-related with no cases in the placebo group. There were no clinically relevant changes in vital signs, electrocardiogram (ECG), or audiometric assessments. By the Week 8 time point (as early as 2 weeks), in the ritlecitinib group, there were decreases in the median platelet counts (25% change from baseline [CFB]), lymphocyte counts (21% CFB), neutrophil counts (17% CFB), and hemoglobin (3% CFB). None of these were deemed to be clinically relevant by the investigator and values returned to near baseline by the 12-week follow-up visit.

Phase 2a Study in Alopecia Areata

Study B7931005 was a Phase 2a, double-blind, placebo-controlled, multi-center study to evaluate the efficacy and safety profile of ritlecitinib and PF-06700841 (a TYK2/JAK1 inhibitor) in participants with moderate to severe alopecia areata. The study consists of the initial 24-week double-blind treatment period (completed), and an ongoing up to 12 months single-blind extension period that includes 6 months of active treatment, that is followed by a 6 months crossover open label extension period. A total of 142 participants were randomized to study treatment; 47 participants received placebo, 48 participants received ritlecitinib, and 47 participants received PF-06700841 in the initial 6 month double-blind treatment period.

The initial 24-week double-blind treatment period has been completed. During this treatment period, participants in the ritlecitinib group were treated with 200 mg of QD during a 4 week induction phase, followed by dosing with 50 mg QD in a maintenance phase. At Week 24, an interim analysis provided data on both efficacy and safety, and indicated clinical improvement for participants treated with ritlecitinib. During the initial 24 week treatment period of Study B7981005, there were no deaths and no participant in the ritlecitinib treatment group experienced a SAE. The proportion of participants who experienced TEAEs in the placebo treatment group (74.5%) was comparable with the ritlecitinib treatment group (66.7%). The TEAEs reported in more than 5% (1 in 20) participants with alopecia areata receiving ritlecitinib were headache, infections of upper respiratory tract, acne, diarrhea, nausea, and skin infections. The majority of events were mild. No serious infections, malignancies, cases of herpes zoster, or cases of herpes simplex were reported in the ritlecitinib group.

Hematological changes were observed in both active groups during the induction and maintenance periods but were not associated with clinically relevant TEAEs. During the induction period, when participants received ritlecitinib 200 mg QD for 4 weeks, decreases in mean platelet and lymphocyte counts (18% and 24% mean CFB, respectively) were observed in the ritlecitinib group. During the maintenance period, when participants received 50 mg QD for 20 weeks, there was improvement in the platelet and lymphocyte counts in the ritlecitinib group.

Two participants in the ritlecitinib group discontinued due to TEAEs. For 1 of the 2 participants assigned to ritlecitinib who discontinued from study treatment due to an AE, the investigator rated the causality as related (angioedema).

Further information regarding clinical experience with ritlecitinib is available in the current version of the IB.

2.3. Benefit/Risk Assessment

Ritlecitinib is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to determine the relationship between TO of JAK3 and the TEC kinase family and the functional consequences of their inhibition overtime by ritlecitinib in healthy participants. These results are expected to provide insights on the mechanism of action for ritlecitinib, and in assessing the impact of ritlecitinib in patients with inflammatory diseases.

In multiple clinical studies, the safety/tolerability profile of ritlecitinib has been extensively characterized and has been shown to have an acceptable safety and tolerability profile. Ritlecitinib is an immune modulator and, as such, can be associated with the potential risk of infections (including serious infections), opportunistic infections, and viral reactivation. The risk of infection from this single dose study is low, but nonetheless participants will be closely monitored in this study.

In the MAD period of the Phase 1 Study of ritlecitinib, the most frequently reported TEAEs across all treatment groups were diarrhea and headache, which were experienced by 8 and 7 participants, respectively. In Phase 2 Study of ritlecitinib in RA patients (B7981006), the most common TEAEs by SOC were Infections and Infestations (6 participants in total, 8.6%). The majority of the all-causality TEAEs were mild in severity. In Phase 2a Study of ritlecitinib and brepocitnib in AA patients (B7931005), the most commonly reported treatment related- TEAEs for ritlecitinib by preferred term were upper respiratory tract infection (6.3%), and acne, nausea,and headache (each at 4.2%).

The expected exposures of ritlecitinib in this study are lower than the highest exposures observed in the SAD/MAD FIH study (see Justification for Dose in Section 4.3). Therefore, the risk to the participants in this study is expected to be minimal. In addition, any risks are minimized by appropriate safety measures including safety laboratory measurements, ECGs, vital signs, and counseling for appropriate use of contraception for study participants.

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

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: Ritlecitinib		
1. Potential risks associated with study intervention include the following: a. transient decrease in leukocyte and platelet counts.	1. The potential risks are based o*n* prior studies for ritlecitinib in healthy participants and RA, AA and vitiligo patients. Details are presented in the IB.	1. Eligibility criteria and study assessments have been selected to ensure that only appropriate participants are included in the study (see Section 5).
Other		
The COVID-19 pandemic may pose risks to study participation.	Participants may have increased risk of SARS-CoV-2 infection by undergoing a study procedure at a study facility.	Inclusion of COVID-19 specific assessments according to the Schedule of Activities and CRU confinement for the entire duration of study.

2.3.2. Benefit Assessment

There is no benefit expected to the participants.

2.3.3. Overall Benefit/Risk Conclusion

Ritlecitinib is not expected to provide any clinical benefit to healthy participants. This study is justified by taking into account measures taken to minimize the potential risks to study participants identified in association with ritlecitinib risk.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To characterize the TO of JAK3 and TEC kinases in PBMCs after single oral dose of ritlecitinib	• Percent TO for JAK3 and TEC kinases (BTK, ITK, RLK, TEC and BMX)
Secondary:	**Secondary:**
• To evaluate the plasma exposure of ritlecitinib over 48 hours after single oral dose administration	• Ritlecitinib plasma PK parameters • C_{max}, T_{max}, C_{last}, C_{av}, AUC_{last}, and AUC_{24}
• To evaluate the safety and tolerability of an oral dose of ritlecitinib when administered alone and in healthy adult participants	• Assessment of TEAEs, clinical laboratory tests, and vital signs
Tertiary:	**Tertiary:**
• To characterize the relationship between TO in PBMCs and plasma ritlecitinib exposure over 48 hours after single oral dose	• Maximal inhibiton (occupancy) by ritlecitinib (TO_{max}) • Ritlecitinib plasma concentrations at 50% TO_{max} (IC_{50})

CCI [redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, single dose, open label, two-arm study to assess TO of JAK3 and TEC kinases by ritlecitinib in healthy adult participants. A total of approximately 16 healthy male and/or female participants, 8 in each cohort, will be enrolled and dosed to achieve at least 6 participants completing each dose level. Participants who discontinue from the study for non-safety reasons may be replaced at the sponsor's discretion.

Participants will be screened within 28 days of the first dose of study medication. Participants will report to the CRU 1 day prior to Day 1 dosing (Day -1).

Participants will be enrolled to receive either 50 mg or 200 mg single dose of ritlecitinib on Day 1. Blood samples to assess ritlecitinib PK, target occupancy and functional assays will be collected over 48 hours. Participants will remain in the CRU until Day 3 when they will be discharged after completion of study related activities as indicated in the SoA.

Participants will have a telephone contact at least 28 calendar days, and up to 35 calendar days after administration of the investigational product(s). At the discretion of the investigator, telephone contact may be substituted with an on-site visit in case of additional follow-up of open AEs or clinically significant laboratory findings. A brief overview of the study is provided in Figure 1.

4.2. Scientific Rationale for Study Design

This study aims to assess the target coverage/TO by ritlecitinib of two distinct families of kinases that are irreversibly bound (JAK3 and TEC kinases). In addition to TO, the study will include an assessment of the effect of ritlecitinib on pathways that functionally depend on either JAK3 or TEC kinases. Together these results enable a more complete assessment of the relative degree of pathway coverage over a broad range of exposures and over a length of time that allows for recycling/production of new target (ie, JAK3 and TEC family kinases).

A parallel design is preferred over a crossover design in this case due to uncertainty around the crossover period washout period due to the unknown duration of downstream effects which are being measuring for the first time in humans.

A single dose study is designed with 2 arms of 50 mg and 200 mg dose of ritlecitinib. The two doses are expected to provide concentrations encompassing those seen at clinically relevant doses in patients with RA, UC, AA and vitiligo. As the PK of ritlecitinib is linear in the clinical dosing range, and steady state/multiple dose exposure-response can be predicted from single doses exposures. Although there is no food-effect, the doses are to be taken under fasted conditions to standardize PK. There is no need for blinding of this single-dose study since the endpoints described above are objective/quantitative and there are no safety concerns that need to be addressed by blinding.

4.2.1. Diversity of Study Population

Not applicable.

4.2.2. Choice of Contraception/Barrier Requirements

Nonclinical studies suggest risk for severe manifestations of developmental toxicity at relevant clinical exposures for ritlecitinib. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.2.3. Collection of Retained Research Samples

Retained Research Samples will be collected and stored for further analyses which may, for example, provide greater understanding of the study intervention.

4.3. Justification for Dose

Single doses of 50 mg and 200 mg are being used in the study. A dose-ranging simulation using a pop-PK model for ritlecitinib[4] showed that the proposed doses in healthy participants would provide, over the 48-hour collection interval, geometric mean C_{48}, C_{max} and C_{avg} concentration that encompasses those from clinical doses in patients with RA, UC, CD, AA or vitiligo (Table 3).

Table 3. Geometric mean C_{48}, C_{max} and C_{avg} for Healthy Participants and Patient Populations Under Evaluation

Population	Dose (mg)	C_{48} (ng/mL)	C_{max} (ng/mL)	C_{avg}(ng/mL)
Healthy	50	BQL	247.44	11.19
Healthy	200	BQL	1085.10	60.57
RA	100	BQL	482.60	51.21
UC	100	BQL	460.24	49.88
AA	50	BQL	256.59	17.07
Vitiligo	50	BQL	263.56	15.12

Based on prior Phase 1 data, 50 mg and 200 mg QD doses of ritlecitinib are expected to be safe and well tolerated in this study. A dose level of 200 mg QD ritlecitinib has demonstrated acceptable safety and tolerability for up to 14 days in healthy participants (B7981001), up to 4 weeks in participants with alopecia areata (B7931005) and up to 8 weeks in RA and UC participants (B7981006 and B7981005). The projected AUC_{48} and C_{max} of 2907 ng•h/mL and 1085 ng/mL at 200 mg single dose provides exposure margin of 3.2- and 2-fold, respectively from NOAEL observed in dogs in second 9-month toxicity study (Highest dose in dogs, 10 mg/kg/day; C_{max} (free) = 1910 ng/mL; $AUC_{24,ss}$ (free) = 7940 ng•h/mL; fu,dog = 0.82, fu,human=0.86).

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure (phone contact) shown in the SoA and any requested unplanned visit(s).

The end of the study (LPLV) is defined as the date the investigator reviews the last participant's final safety data and determines that no further evaluation is required for the participant to complete the trial.

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 the following criteria apply:

Age and Sex:

1. Male and female participants must be 18 to 60 years of age, inclusive, 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 overtly healthy as determined by medical evaluation including medical history, physical examination including BP and pulse rate measurement, 12-lead ECG, or clinical and laboratory 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 30.5 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. Infection with HIV, hepatitis B or hepatitis C viruses according to protocol-specific testing algorithm. For HIV, hepatitis B and hepatitis C, all participants will undergo testing for HIV, HBsAg, HBcAb and HCVAb during Screening. Please refer to Appendix 2 for testing algorithm, reflex testing, and full eligibility criteria.

4. Have evidence of untreated or inadequately treated active or latent Mycobacterium TB infection as evidenced by the following:

    - A positive QFT-G test performed within the 12 weeks prior to screening. IF the laboratory reports the test as indeterminate, the test should be repeated. If the result of the repeat test is indeterminate, a PPD test may be substituted for the QFT-G test only with approval from the Pfizer Medical Monitor on a case-by-case basis.

    - History of either untreated or inadequately treated latent or active TB infection.

        - If a participant has previously received an adequate course of therapy for either latent (9 months of isoniazid in a locale where rates of primary multidrug resistant TB infections are <5% or an acceptable alternative regimen) or active (acceptable multi-drug regimen) TB infection, neither a QFT-G test nor a PPD test need to be obtained. Details of previous course of therapy (eg, medication(s) used, dose, duration of therapy) should be documented in the source documentation.

        - A participant who is currently being treated for active or latent TB infection must be excluded from the study.

5. Participants with any of the following acute or chronic infections or infection history:

    - Any infection requiring treatment within 2 weeks prior to the screening visit.

    - Any infection requiring hospitalization, parenteral antimicrobial therapy within 60 days of the first dose of investigational product.

- Any infection judged to be an opportunistic infection or clinically significant by the investigator, within the past 6 months of the first dose of the investigational product.

- Known active or history of recurrent bacterial, viral, fungal, mycobacterial or other infections.

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

6. History of febrile illness within 5 days prior to the first dose of investigational product.

7. History of any lymphoproliferative disorder such as EBV related lymphoproliferative disorder, history of lymphoma, history of leukemia, or signs and symptoms suggestive of current lymphatic or lymphoid disease.

8. Participants have a known present or a history of malignancy other than a successfully treated or excised non metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.

9. Vaccination with live virus, attenuated live virus, or any live viral components is prohibited within the 6 weeks prior to the first dose of study intervention, during the study, and for 6 weeks after the last dose of study intervention. Similarly, current routine household contact with individuals who have been vaccinated with live vaccine components should be avoided during treatment and for 6 weeks following completion of treatment. Following vaccination with live component vaccines, the virus may be shed in bodily fluids, including stool, and there is a potential risk that the virus may be transmitted.

   Such vaccines include but are not limited to: FluMist® (intranasal influenza vaccine), attenuated rotavirus vaccine, varicella (chickenpox) vaccine, attenuated typhoid fever vaccine, oral polio vaccine, MMR vaccine, vaccinia (smallpox) vaccine, and Zostavax® (zoster vaccine live).

10. Have received only one of the 2 required doses of COVID-19 vaccine.

11. Other medical or psychiatric conditions including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality, or other conditions or situations related to COVID-19 pandemic (eg, Contact with positive case, residence, or travel to an area with high incidence) that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

12. 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 Concomitant Therapy for additional details).

Prior/Concurrent Clinical Study Experience:

13. 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).

14. Known participation in a clinical trial of ritlecitinib within 30 days prior to the first dose of study medications.

15. Known participation in a clinical trial of ritlecitinib and participant experienced treatment-related adverse events that led to discontinuation or an SAE (≥ CTCAE Grade 3).

Diagnostic Assessments:

16. A positive urine drug test.

17. 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.

18. 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.

19. 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;

- Total bilirubin 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≤ ULN.

- Hemoglobin level ≤135 g/L (13.5 g/dL) for males and ≤120 g/L (12.0 g/dL) for females.

- Platelet count ≤100×10^9/L (100,000 cells/mm3) or ≥1000×10^9/L (1,000,000 cells/mm^3).

- WBC count ≤3.0 × 109/L (3000 cells/mm^3) or ANC <1500 cells/mm3 or ALC <800 cells/mm^3.

- eGFR ≤60 mL/min/1.73m^2 based on CKD-EPI equation.

Other Exclusions:

20. 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).

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

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

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

24. 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 24 hours prior to the start of dosing until collection of the final PK sample.

- 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. 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 24 hours prior to dosing and during confinement in the CRU.

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 and his or her partner(s) from the permitted list of contraception methods (see Appendix 4 Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the schedule of activities (SoA), the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception) 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 by 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.

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 Ritlecitinib.

6.1. Study Intervention(s) Administered

For this study, the investigational product is ritlecitinib.

The 50 mg dose will be administered as a single 50 mg capsule and the 200 mg dose as four 50 mg capsules which will be supplied to the CRU in bulk along with individual dosing containers for unit dosing. Investigational product will be presented to the participants in individual dosing containers.

6.1.1. Administration

Following an overnight fast of at least 10 hours, participants will receive study intervention at approximately 0800 hours (plus or minus 2 hours) on Day 1. 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.

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.

6.1.2. Medical Devices

Not applicable.

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 PCRU local/site procedures.

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 PCRU's local/site procedures. 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 identification 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.

Capsules will be prepared at the CRU in the individual dosing containers by 2 operators, 1 of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). The capsules will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical 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.

6.3.2. Breaking the Blind

Not applicable.

6.4. Study Intervention Compliance

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

6.5. Dose Modification

No dose changes/adjustments including flexible dosing; dose reductions, interruptions, or tapering is allowed as per study protocol.

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

Not applicable.

6.7. Treatment of Overdose

For this study, any dose of ritlecitinib greater than 800 mg within a 24-hour time period will be considered an overdose.

There is no specific treatment for an overdose with ritlecitinib.

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 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 7 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

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.

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

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 Ritlecitinib; 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

Since this is a single dose study, this section is not applicable.

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 safety, behavioral, compliance, or administrative reasons.

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

The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

The participant will be permanently discontinued from the study intervention and the study at that time.

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. In addition, other clinical assessments or specimen collections, eg, banked biospecimens, may be used without repeat collection, as appropriate.

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 380 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. Respiratory Rate

Not applicable.

8.2.2.2. Temperature

Not applicable.

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 heart rate 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 the safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) a post dose QTcF interval is increased by ≥60 msec from the baseline **and** is >450 msec; or b) an absolute 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 post dose QTcF interval remains ≥60 msec from the baseline **and** is >450 msec; or b) an absolute 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.

8.2.3.1. Continuous Cardiac Monitoring by Telemetry

Not applicable.

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 to 35 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.

8.2.5. COVID-19 Specific Assessments

Participants will be tested for SARS-CoV-2 infection by PCR prior to being admitted to the clinic for confinement and a subsequent COVID-19 test will be performed after 4 days (ie, upon completion of 4 x 24 hours in house), or if they develop COVID-19 like symptoms. Additional testing may be required by local regulations or by the Principal Investigator.

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 to 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. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.2.7. Suicidal Ideation and Behavior Risk Monitoring

Not applicable.

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 Ritlecitinib (see Section 7.1).

During the active collection period as described in Section 8.3.1, each participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative) 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, except as indicated below, 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 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.

Reporting of AEs and SAEs for participants who fail screening are subject to the CRF requirements as described in Section 5.4.

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 exposure during pregnancy, exposure during breastfeeding, and occupational exposure.

Any such exposure to the study intervention under study is 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 male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.

- 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 ingestion.

    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion 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 a minimum of 28 calendar days after 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 liveborn 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 exposure during breastfeeding 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 exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by ingestion.

The investigator must report exposure during breastfeeding 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 exposure during breastfeeding 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 exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

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

This section is not applicable because efficacy is not expected in the study population.

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 clinical trial settings, such as medication errors.

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

Medication errors include:

- Medication errors involving participant exposure to the 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 and Pharmacodynamics

8.4.1. Pharmacokinetics

For the measurement of ritlecitinib concentrations, blood samples of 2 mL to provide approximately 0.5 mL of plasma will be collected into appropriately labeled tubes containing K_2EDTA (dipotassium ethylenediaminetetraacetic acid) at times specified in the SoA. Instructions for the collection and handling 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.

Samples will be used to evaluate the PK of ritlecitinib. Samples collected for analyses of ritlecitinib concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

Genetic analyses will not be performed on these plasma samples (unless consent for this was included in the informed consent). Participant confidentiality will be maintained.

Samples collected for measurement of plasma concentrations of ritlecitinib will be analyzed using a validated analytical method in compliance with applicable SOPs.

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.

8.4.2. Pharmacodynamics

The following samples for pharmacodynamics are required and will be collected from all participants in this study as specified in the SoA:

- Target occupancy blood sample.

CCI [redacted]

8.4.2.1. Target Occupancy:

Whole blood samples (approximately 30 mL) will be collected according to the timepoints specified in the SoA in sodium heparin tubes. PBMCs will be lysed and protein will be isolated. An ATP-competitive probe will be used to pull-down kinases that are not covalently bound to PF-06651600. Protein isolate will be digested with trypsin and unique peptides within JAK3, BMX, BTK, ITK, TEC and TXK have been identified and will be used to quantitate the amount of each kinase that is not occupied by ritlecitinib.

CCI [redacted]

8.5. Genetics

8.5.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

8.5.2. Retained Research Samples for Genetics

A 4-mL blood sample optimized for DNA isolation Prep D1 will be collected according to the SoA, as local regulations and IRBs/ECs allow.

CCI [redacted]

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in lab manual and other supporting documentation.

8.6. Biomarkers

Biomarkers evaluated in this study are detailed in Section 8.4.2.

8.6.1. Retained Research Samples for Biomarkers

Retained Research Samples for biomarker analysis will not be collected in this study.

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 safety or PK data.

9.2. Analysis Sets

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

Population	Description
Enrolled	All participants who sign the ICD.
Randomly assigned to investigational product	All participants who sign the ICD and meet all eligibility criteria.
Evaluable	The PK concentration population is defined as all participants enrolled and treated who have at least 1 concentration of ritlecitinib. The PD population is defined as all enrolled and treated who have at least 1 TO measurement.
Safety Analysis Set	All participants who take at least 1 dose of investigational product.

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, secondary CCI [redacted] endpoints.

9.3.1. Primary Endpoints

The primary endpoint in human PBMCs is TO of JAK3, BTK, ITK, RLK, TEC and BMX after a single dose of ritlecitinib. Target occupancy for each kinase at time *t* will be evaluated as follows:

$$\%\,Target\ Occupancy_t = 100\,\% - \%\,Free\ Target_t$$

with TO_0 as the baseline variable of target occupancy, which is the mean of the two pre-dose measurements at Hour -1 and Hour 0 on Day 1. If only one of the two pre-dose measurements is available, TO_0 is the available pre-dose measurement.

TO profiles will be assessed graphically and summarized by nominal timepoints using descriptive statistics.

9.3.2. Secondary Endpoints

The secondary endpoints are pharmacokinetic parameters of ritlecitinib after single oral dose.

PK parameters will be derived, given available data, following single dose administration from the concentration-time profiles for ritlecitinib as follows:

Parameter	Definition	Method of Determination
AUC_{24}	Area under the plasma concentration-time curve from time 0 to 24 hours	Linear/Log trapezoidal method
AUC_{last}	Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
C_{av}	Average plasma concentration from time 0 to the time of the last quantifiable concentration	$AUC_{24}/24$
C_{max}	Maximum plasma observed concentration	Observed directly from data
C_{last}	Plasma concentration at 48 hours post-dose	Observed directly from data
T_{max}	Time to reach C_{max}	Observed directly from data as time of first occurrence

Concentrations will be assessed graphically. Concentrations (by nominal timepoints) and PK parameters will be summarized using descriptive statistics.

9.3.3. Tertiary Endpoints

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The relationship between TO and plasma exposure of ritlecitinib will be assessed graphically. If a trend in the relationship between drug plasma concentration and TO is observed, a suitable exposure-response population model (eg, Turnover models) may be utilized to further quantify the relationship.[5,6]

CCI

9.3.4. Safety Analyses

All safety analyses will be performed on the safety population.

AEs, 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.

9.3.4.1. Electrocardiogram Analyses

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

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

Safety QTc Assessment

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

9.3.5. Other Analyses

Pharmacogenomic data from Retained Research Samples may be collected during the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

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, facilitating PK/PD modeling, and/or supporting clinical development.

9.5. Sample Size Determination

A sufficient number of participants will be screened to achieve 8 participants enrolled to study intervention for an estimated total of at least 6 evaluable participants per dose level. The sample size of this study (2 arms, approximately 8 participants per arm, up to approximately 16 completers) was selected based on clinical consideration to adequately characterize the TO of JAK3 and TEC kinases, and PK/PD considerations and on the need to minimize exposure to healthy participants at each dose level. No formal inferential statistics would be applied to the TO, PK/PD and safety data.

Dropouts may be replaced at the discretion of the sponsor and investigator, unless the reason for drop-out is a clinically relevant drug-related safety or tolerability event.

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 Medical Device Regulation 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

Not applicable.

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.

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

10.1.4. Data Protection

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

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password-protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site 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 clinical trial 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 clinical trial 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 European Union 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 by 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 IQMP 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 Source Document Locator, which is maintained by the sponsor's designee (PCRU).

Description of the use of the computerized system is documented in the Source Document Locator, which is maintained by the sponsor's designee (PCRU).

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.

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 CTMS. 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 identification number, (c) site emergency phone number active 24 hours/day, 7 days per week.

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.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests (Table 4) will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

At screening, HbsAg and HbcAb will be tested:

a. If both tests are negative, the participant is eligible for study inclusion;

b. If HbsAg is positive, the participant must be excluded from participation in the study;

c. If HbsAg is negative and HbcAb is positive, HbsAb reflex testing is required:

   i. If HbsAb is negative, the participant must be excluded from participation in the study;

   ii. If HbsAb is positive, the participant is eligible for study inclusion.

See Section 7.1 for more information on participant safety monitoring and discontinuation regarding clinical lab tests.

Table 4. 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 Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT TBili Alkaline phosphatase Uric acid Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	• Urine drug screening[b] • Pregnancy test (β-hCG)[c] • eGFR (CKD-EPI) At screening only: • Serum FSH[d] • HBsAg/HBcAb • HCVAb[e] • HIV • QFT-G (IGRA)

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 and study specific).

c. Local serum testing will be standard for the protocol. Serum or urine β-hCG for female participants of childbearing potential.

d. For confirmation of postmenopausal status only.

e. All participants will undergo testing for HCVAb during Screening.

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/plasma 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. Upon completion of the study, these retained safety samples may be used for the assessment of exploratory safety biomarkers or unexpected safety findings. These data will not be included in the CSR. Samples to be used for this purpose will be shipped to either a Pfizer-approved BBS facility or other designated laboratory and retained for up to 1 year following the completion of the study.

IGRA

QFT-G will be performed during screening. Blood sampling may include 3 mL up to 10 mL of blood. Test should be performed in accordance with the product specific processing and analyzing instructions.

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), symptoms, 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 drug- interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE 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 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 exposure during pregnancy 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 a 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 data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (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 data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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

- Refrain from donating sperm.

PLUS either**:**

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

  OR

- Must agree to use contraception/barrier as detailed below:

  - Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.

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

10.4.2. Female Participant Reproductive Inclusion Criteria

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

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

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), 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). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

A WOCBP agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. 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 not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female.

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

10.4.4. Contraception Methods

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

Highly Effective Methods That Have Low User Dependency

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

2. Intrauterine device.

3. Intrauterine hormone -releasing system.

4. Bilateral tubal occlusion (eg, bilateral tubal ligation).

5. Vasectomized partner.

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

Highly Effective Methods That Are User Dependent

6. 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.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.

- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.

- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to study intervention or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

- The results of genetic analyses may be reported in the CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.

- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

    - Retained samples will be stored indefinitely or for another period as per local requirements.

- Participants may withdraw their consent for the storage and/or use of their Retained Research Samples at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.

- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

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 co-formulated 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 (absolute) or by ≥60 msec from baseline.
- New onset- atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm.
- New onset type I second degree (Wenckebach) AV block of >30 seconds' duration.
- Frequent 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 left bundle branch block (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 (heart rate <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm (such as torsade's 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: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents (TOC). The protocol amendment summary of changes tables for past amendment(s) can be found below:

Amendment 1 (01-October-2021)

Overall Rationale for the Amendment: This amendment is to enunciate details of clarifications CCI and statistical analysis.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis: Objectives and Endpoints and CCI	1. Removal of "%" from primary endpoint CCI	1. Typographic error, removed to avoid repetition CCI
1.1 Synopsis: Statistical Methods	1. Replace "Baseline corrected TO" with "Percent TO" CCI	1. Clarification of primary CCI endpoint statistical methods
CCI		

Section # and Name	Description of Change	Brief Rationale
2.2.1 Nonclinical Pharmacology	Addition of "RLK"	Clarification of TEC enzymes
5.2 Exclusion Criteria	1. Exclusion Criteria # 3, addition of "HIV" 2. Exclusion Criteria # 14, replace "90 days" with "30 days"	1. Clarification of HIV screening as shown in SoA and Table 6 2. To facilitate subject recruitment for those with known participation in a clinical trial of ritlecitinib
8. Study Assessments and Procedures	Replace "350 mL" with "380 mL"	Update on blood volume required to accommodate JAK3 inhibition assay
8.4.2 Pharmacodynamcics	1. Addition of section 8.4.2.1. for Target Occupancy assay CCI [redacted]	For clarification of various pharmacodynamic assays CCI [redacted]
9.3.1 Primary Endpoints	1. Addition of "for each kinase" 2. Addition of "with TO_0 as the baseline variable of target occupancy, which is the mean of the two pre-dose measurements at Hour -1 and Hour 0 on Day 1. If only one of the two pre-dose measurements is available, TO_0 is	Clarification of statistical methods for primary endpoint

Section # and Name	Description of Change	Brief Rationale
	the available pre-dose measurement." 3. Deleted "Baseline corrected"	
CCI [redacted]		
10.1.11. Sponsor's Qualified Medical Personnel	1. Delete "and (d) Pfizer Call Center number" 2. Delete "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"	Template modification
10.2. Appendix 2: Clinical Laboratory Tests	1. Replaced "QuantiFERON TB Test" with QFT-G 2. Replaced Interferon Gamma Release Assay with "IGRA"	To maintain consistency in the protocol

10.9. Appendix 9: Abbreviations

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

Abbreviation	Term
AA	alopecia areata
Abs	absolute
ADL	activities of daily living
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{24}	area under the plasma concentration time profile from time 0 to 24 hours
$AUC_{24,ss}$	area under the plasma concentration time profile from time 0 to 24 hours at steady state
AUC_{48}	area under the plasma concentration time profile from time 0 to 48 hours
AUC_{inf}	area under the plasma concentration time profile from time 0 extrapolated to infinity
AUC_{last}	area under the plasma concentration time profile from time 0 to the time of the last quantifiable concentration
AUC_{tau}	area under the plasma concentration-time profile from time 0 to time tau, the dosing interval
AV	atrioventricular
BA	bioavailability
BAEP	brainstem auditory evoked potential
BBS	Biospecimen Banking System
BCR	B cell receptor
BCRP	breast cancer resistance protein
BESP	bile salt export pump
β-hCG	beta human chorionic gonadotropin
BID	twice a day
BMI	body mass index
BMX	bone marrow tyrosine kinase gene in chromosome X
BP	blood pressure
BPM	beats per minute
BSEP	bile salt export pump
BTK	Bruton's tyrosine kinase
BUN	blood urea nitrogen
C_{av}	Average plasma concentration from time 0 to the time of the last quantifiable concentration

Abbreviation	Term
CD	cluster of differentiation
CFB	change from baseline
CFR	Code of Federal Regulations
CI	confidence interval
CIA	collagen induced arthritis
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{last}	Plasma concentration at 48 hours post-dose
CL/F	apparent clearance
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
CMV	Cytomegalovirus
CNS	central nervous systems
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
CT	clinical trial
CTCAE	common terminology criteria for adverse events
CTMS	clinical trial management system
CYP	cytochrome P450
D	day
DDI	drug-drug interaction
DILI	drug induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
EBV	Epstein barr virus
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
EFD	embryo-fetal developmental
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EPO	erythropoietin
ET	early termination

Abbreviation	Term
EU	European Union
EudraCT	European Clinical Trials Database
F	absolute oral bioavailability
Fa	fraction absorbed
FACS	fluorescence activated cell sorting
FIH	first in human
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GI	gastrointestinal
GLP	Good Laboratory Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HCVAb	hepatitis C antibody
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
HS	hidradenitis suppurativa
HSV	herpes simplex virus
hWB	human whole blood
IB	investigator's brochure
IC_{50}	50% inhibitory concentration
ICD	informed consent document
ICH	International Council for Harmonisation
IgD	Immunoglobulin D
IGRA	Interferon Gamma Release Assays
IL	interleukin
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IQMP	Integrated Quality Management Plan
IR	immediate release
IRAK4	interleukin 1 receptor associated kinase 4
IRB	institutional review board
ITK	IL 2 inducible T-cell kinase
IUD	intrauterine device
IV	intravenous

Abbreviation	Term
JAK	Janus kinase
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LBBB	left bundle branch block
LFT	liver function test
LPLV	last participant last visit
MAD	multiple ascending dose
MATE	multidrug and toxin extrusion protein
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
CCI	[redacted]
MMR	measles, mumps, and rubella combination vaccine
MR	modified-release
mRNA	messenger RNA
msec	milli-second
NADPH	nicotinamide adenine dinucleotide phosphate
N/A	not applicable
NK	natural killer
NOAEL	No-observed-adverse-effect level
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
PBMC	Peripheral blood mononuclear cells
PCR	polymerase chain reaction
PCRU	Pfizer clinical research unit
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
pH	potential of hydrogen
PK	pharmacokinetic(s)
PNS	peripheral nervous systems
PPD	purified protein derivative
PR	PR interval
PT	prothrombin time
PTR	peak-to-trough ratio
PVC	premature ventricular contraction/complex
QD	once daily
QFT-G	QuantiFERON Gold-TB test
QID	4 times a day
QRS	QRS interval
QTc	corrected QT
QTcF	corrected QT (Fridericia method)

Abbreviation	Term
qual	qualitative
RA	rheumatoid arthritis
RLK	resting lymphocyte kinase
RBC	red blood cell
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCr	serum creatinine
SoA	schedule of activities
SOC	system organ class
SOP	standard operating procedure
SRSD	single reference safety document
CCI	[redacted]
SULT	sulfotransferases
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	half-life
TB	tuberculosis
TBili	total bilirubin
TBNK	T cell, B cell, natural killer cell
TCR	T cell receptor
TEAE	treatment emergent adverse event
TEC	tyrosine kinase expressed carcinoma
THC	tetrahydrocannabinol
TK6	thymidine kinase-6
TLR	toll--like receptor
T_{max}	time for C_{max}
TO	target occupancy
TO_{max}	maxmum target occupancy
TXK	tyrosine kinase expressed in T cells
TYK	tyrosine kinase
UC	Ulcerative colitis
UDP	glucuronosyltransferase
UGT	glucuronosyltransferase
ULN	upper limit of normal
US	United States
VZV	Varicella zoster virus
WBC	white blood cell
WOCBP	woman/women of childbearing potential

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