PHASE 1, OPEN-LABEL, FIXED-SEQUENCE, 2-PERIOD STUDY TO ESTIMATE THE EFFECT OF MULTIPLE-DOSE RITLECITINIB (PF-06651600) ON THE PHARMACOKINETICS OF SINGLE-DOSE TOLBUTAMIDE IN HEALTHY PARTICIPANTS

Study Intervention Number:	PF-06651600
Study Intervention Name:	Ritlecitinib
US IND Number:	131,503
EudraCT Number:	2021-003611-25
ClinicalTrials.gov ID:	Not Applicable
Protocol Number:	B7981069
Phase:	1

Short Title: Open-Label, Fixed-Sequence, 2-Period Study to Evaluate the Effect of Multiple-Dose Ritlecitinib on the PK of Tolbutamide

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Document History

Document	Version Date
Amendment 1	17 September 2021
Original protocol	14 July 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 1 (17-September-2021)

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Exclusion Criteria #17	Update Exclusion Criteria #17 to "Known participation in a clinical trial of ritlecitinib and the participant experienced a ritlecitinib-related AE that led to discontinuation or had a ritlecitinib-related SAE."	The portion of the exclusion criterion that prohibited participation in a ritlecitinib study during the 60 days prior to the first dose of investigational product in B7981069 has been removed. The study team determined that the expected follow-up periods included in prior ritlecitinib studies that participants may be involved in, together with the screening period into this study, would be sufficient to allow for washout of ritlecitinib from previous studies and for a return of any impacted drug metabolizing enzymes from previous studies to their baseline activity.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Brief Title: Open-Label, Fixed-sequence, 2-Period Study to Evaluate the Effect of Multiple-Dose Ritlecitinib on the PK of Tolbutamide

Rationale

This is a Phase 1, 2-period, multiple-dose, open-label, single fixed sequence study of the effect of ritlecitinib on tolbutamide pharmacokinetics in healthy participants. A total of approximately 12 healthy male and/or female participants will be enrolled in the study to obtain at least 10 evaluable participants who complete the study. The study is designed as a fixed sequence study to avoid the long washout period needed in a crossover design due to long half-lives of CYP enzymes to revert back to their baseline values. The fixed-sequence design has a low risk of period effect. This is an open-label study not requiring an assessment of efficacy or pharmacodynamics markers, but it will include PK estimation DDIs.

Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
• To evaluate the effect of multiple-dose ritlecitinib (PF-06651600) on the PK of a single, oral dose of tolbutamide in healthy participants.	• C_{max} and AUC_{inf} (if data permit, otherwise AUC_{last}) of tolbutamide.
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of ritlecitinib when coadministered with a single dose of tolbutamide.	• Incidence of treatment-emergent adverse events
Other/Exploratory:	**Other/Exploratory:**
• To characterize the PK of a single oral dose of tolbutamide in healthy participants.	• Plasma tolbutamide PK parameters:T_{max}, AUC_{last}, CL/F, V_Z/F and $t_{½}$, as data permit.

Overall Design

Brief Summary

This is a Phase 1, 2-period, multiple-dose, open-label, single fixed sequence study of the effect of ritlecitinib on tolbutamide pharmacokinetics in healthy participants. A total of approximately 12 healthy male and/or female participants will be enrolled in the study to obtain at least 10 evaluable participants who complete the study. Participants who withdraw from the study or are considered non-evaluable may be replaced at the discretion of the sponsor.

Participants will be screened within 28 days of the first dose of study medication. Participants will report to the CRU the day prior to Day 1 dosing (Day -1) in Period 1 for both treatment sequences. Participants will remain in the CRU for a total of 16 days and 15 nights. This includes 4 days and 4 nights (starting the night of admission to the CRU) in Period 1 and 12 days and 11 nights in Period 2. There will be no washout period between 2 treatment periods.

In Period 1, participants will be dosed with a single administration of tolbutamide 500 mg tablet on Day 1. Tolbutamide PK will be assessed for 36 hours following dosing. Period 1 will be immediately followed by Period 2 with no washout. In Period 2, participants will be dosed with oral 200 mg ritlecitinib QD for 10 days followed by administration of a single dose of 500 mg tolbutamide oral tablet within approximately 5 minutes after administration of a 200 mg dose of ritlecitinib on the morning of Day 10. Tolbutamide PK in Period 2 will again be assessed at pre-dose and over 36 hours after tolbutamide dosing. Dosing with oral 200 mg ritlecitinib QD will continue through Day 10.

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

Number of Participants

Approximately 12 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

In Period 1, participants will be dosed with a single administration of tolbutamide 500 mg tablet on Day 1. Period 1 will be immediately followed by Period 2 with no washout. In Period 2, participants will be dosed with oral 200 mg ritlecitinib QD for 10 days followed by administration of a single dose of 500 mg tolbutamide oral tablet within approximately 5 minutes after administration of a 200 mg dose of ritlecitinib on the morning of Day 10.

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

Data Monitoring Committee or Other Independent Oversight Committee: No.

Statistical Methods

There is no formal research hypothesis to be statistically tested for this study. The purpose of this study is to estimate the PK effect, as well as safety and tolerability of multiple-dose ritlecitinib with a single, oral dose of tolbutamide in healthy participants.

Natural log transformed AUC_{inf}, AUC_{last}, and C_{max} of tolbutamide will be analyzed using a mixed effect model with treatment as a fixed effect and participant as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. Tolbutamide alone will be the Reference treatment, while the tolbutamide co-administered with ritlecitinib will be the Test treatment.

1.2. Schema (Not Applicable)

1.3. Schedule of Activities

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

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

Table 1. Schedule of Activities

	Screening	Period 1				Period 2							FU Phone Call	ET
Visit Identifier[a] Abbreviations used in this table may be found in Section 10.9	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 1**	**Day 2**	**Day 3 to Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**28-35 Days after Last Dose**[n]	
Informed consent	X													
Inclusion/Exclusion Criteria	X													
CRU confinement		X	→	→	→	→	→	→	→	→	→	X		
Medical, drug, tobacco and alcohol history	X	X												
Demography	X													
Complete/limited physical examination[b]	X	X										X[o]		X[o]
Safety laboratory[c]	X	X			X				X			X		X
TB screening[d]	X													
Serum FSH (postmenopausal women only)	X													
Pregnancy test (for WOCBP only)[e]	X	X										X		X
Serology: HBsAg, HBcAb, HCV Ab, and HIV[f]	X													

Table 1. Schedule of Activities

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Visit Identifier[a] Abbreviations used in this table may be found in Section 10.9	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 1**	**Day 2**	**Day 3 to Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**28-35 Days after Last Dose**[n]	
Collection of baseline sample for potential viral screens[g]		X												
Retained Research Sample for Genetics (Prep D1)[h]			X											
Retained Research Sample for Biomarkers (Prep B2)[h]			X											
Genotyping for CYP2C9[h]			X											
Urine drug screen	X	X												
COVID-19 testing	X	X				X								X
COVID-19 temperature check	X	X	X	X	X	X	X	X	X	X	X	X		X
COVID-19 check questionnaire	X	X												X
Single 12-Lead ECG[i]	X		X									X		X
Vital signs (supine BP, pulse rate and oral temperature)[i]	X		X									X		X
Contraception check	X	X										X	X	X
Tolbutamide dosing			X[j]							X[k]				
Ritlecitinib QD dosing						X	X	X	X	X[k]				
Tolbutamide PK blood samples[l]			X	X						X	X			
Serious and non-serious AE monitoring[m]	X	→	→	→	→	→	→	→	→	→	→	X	X	X
Prior/concomitant treatment assessment	X	→	→	→	→	→	→	→	→	→	→	X		X
CRU discharge												X		

Table 1. Schedule of Activities

	Screening	Period 1				Period 2							FU Phone Call	ET
Visit Identifier[a] Abbreviations used in this table may be found in Section 10.9	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 1**	**Day 2**	**Day 3 to Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**28-35 Days after Last Dose**[n]	

a. Day relative to start of study treatment (Day 1).
b. Complete physical examination can be performed either at Screening or Day -1 of Period 1. See Section 8.2.1.
c. Safety laboratory samples will be collected following an overnight fast of at least 12 hours.
d. TB screening will utilize IGRA. Details of eligibility are described in Appendix 2.
e. 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.
f. All participants will undergo screening for Hepatitis B and Hepatitis C for eligibility. Please refer to Appendix 2 for testing algorithm, reflex testing, and full eligibility criteria.
g. A serum sample will be collected at baseline and submitted to the central lab. The sample will be stored and analyzed at a later date only at the sponsor's request. For example, in certain cases of suspected viral infection (eg, disseminated herpes zoster or varicella), the sponsor may request to analyze the sample to determine if the subject had exposure to that virus.
h. 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.
i. ECG and vital signs will be collected before dosing on Day 1 of Period 1 and on Day 12 of Period 2.
j. Participants will be dosed with tolbutamide within approximately 10 minutes of completion of a standard breakfast.
k. On the day of co administration of tolbutamide and ritlecitinib, within approximately 10 minutes of completion of a standard breakfast, the dosing will be administered at approximately 08:00 ±2 hours. Ritlecitinib will be administered first. After swallowing the ritlecitinib dose, tolbutamide should be administered within approximately 5 minutes.
l. PK blood samples are to be collected at pre-dose, at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, and 36 hours post-dose in Periods 1 and 2.
m. All potential treatment related events of rash will be followed up until resolution or agreement with Pfizer. See Section 10.8.1.
n. Participants will have a telephone contact between 28 calendar days and 35 calendar days after the last administration of the investigational product.
o. Limited physical exam as deemed appropriate by the investigator.

Table 2. Pharmacokinetic Sampling Schema

Study Day for Period 1	**1**											**2**	
Study Day for Period 2	**10**											**11**	
Hours After Dose	**0**	**0.5**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**24**	**36**
Tolbutamide administration	X												
Tolbutamide PK blood sampling	X[a]	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: PK = pharmacokinetic.

a. Pre-dose sample.

2. INTRODUCTION

Ritlecitinib (PF-06651600) is a selective covalent inhibitor of JAK3 and the tyrosine kinase expressed in TEC family kinases and is currently under development for the treatment of AA, RA, vitiligo, UC, and CD.

2.1. Study Rationale

The purpose of the study is to estimate the inductive effect of multiple-dose ritlecitinib on single dose PK of tolbutamide. In vitro studies indicated mild induction potential of ritlecitinib for CYP3A4 (R 0.08), CYP2B6 (R 0.23), CYP1A2 (R 0.07), CYP2C8 (R 0.06), CYP2C9 (R 0.29), and CYP2C19 (R 0.32) enzymes, where R represents the predicted ratio of intrinsic clearance values of a probe substrate for an enzymatic pathway in the absence and presence of an inducer. The effect of ritlecitinib on CYP3A4 and CYP2B6 was evaluated in a drug interaction study with coadministration of both sensitive CYP3A substrate, midazolam, and sensitive CYP2B6 substrate, efavirenz (B7981017), and the results indicated that ritlecitinib is a moderate CYP3A inhibitor and does not affect CYP2B6 enzymes. The CYP2C enzymes are regulated by pregnane X receptor (PXR) pathway, which regulates CYP3A enzymes as well.[1] Study B7981017 results implied the net effect of ritlecitinib on CYP3A from both enzyme induction and inhibition, and enzyme induction risk of ritlecitinib through PXR pathway cannot be completely ruled out. Therefore, a DDI study assessing the ritlecitinib effect on the in vivo pharmacokinetics of a sensitive CYP2C substrate needs to be conducted to rule out an inducive effect on the aforementioned isoenzymes.

Tolbutamide is a first generation sulphonylurea developed for treatment of diabetes mellitus. When administered orally, tolbutamide is readily absorbed from the gastrointestinal tract. Absorption and pharmacodynamic effects of tolbutamide are not impacted by food. Detectable levels of tolbutamide are present in the plasma within 20 minutes after oral ingestion of a 500 mg tolbutamide tablet, with peak levels occurring at 3 to 4 hours and minimal amounts detectable at 24 hours. The half-life of tolbutamide is 4.5 to 6.5 hours. Tolbutamide is mainly metabolized by CYP2C9 and acts as a sensitive substrate for this isoenzyme.[2,3] Tolbutamide metabolites are eliminated renally. The current study is designed to estimate any inductive effect of PF-06651600 on the pharmacokinetics of tolbutamide.

2.2. Background

Ritlecitinib is a covalent and irreversible inhibitor of JAK3 with high selectivity over the other 3 JAK isoforms (JAK1, JAK2, and TYK2). Ritlecitinib also inhibits irreversibly the tyrosine kinase expressed in TEC family kinases with selectivity over the broader human kinome. Treatment with ritlecitinib is expected to inhibit the inflammatory pathways mediated by IL-7, IL-15, and IL-21, all implicated in UC, AA, RA, CD and vitiligo. Due to lack of activity against the other JAK isoforms, ritlecitinib is expected to spare immunoregulatory cytokines such as IL-10, IL-27 and IL-35, which are critical to the maintenance of immunosuppressive functions and immune homeostasis.

2.2.1. Nonclinical Pharmacology

Details of the nonclinical pharmacology of ritlecitinib can be found in the current IB for ritlecitinib.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

Details of the nonclinical PK and metabolism of ritlecitinib can be found in the current ritlecitinib IB.

2.2.3. Nonclinical Safety

Based on the absence of adverse effects at the highest dose tested, the NOAEL in the 8-week dog study was 45 mg/kg/day. In the first 9-month dog study, the NOAEL was 5 mg/kg/day, the lowest dose tested, based on the adverse finding of axonal dystrophy in the brainstem and associated waveform defects in males and females administered ≥20 mg/kg/day, the next highest dose used in that study. In the second 9-month dog toxicity study, the NOAEL was 10 mg/kg/day, based on adverse over-immunosuppression and axonal dystrophy in the CNS and PNS at ≥20 mg/kg/day, accompanied by functional auditory deficits (BAEP) at the highest dose of 40 mg/kg/day. The 10 mg/kg/day dose corresponded to a mean AUC_{24} of 7940 ng•h/mL and exposure margins were 6.5x and 1.5x the AUC_{24} at the 50 mg and 200 mg clinical doses, respectively.

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

2.2.4. Clinical Overview

2.2.4.1. Clinical Overview of Ritlecitinib

Ritlecitinib has been explored in healthy participants in 14 Phase 1 trials including an FIH Study B7981001 study, a relative BA study of oral solution formulation of ritlecitinib relative to tablets (B7981003), a PK study in Japanese participants (B7981008), an ADME study (B7981011), a drug interaction study with midazolam and efavirenz (B7981017), a drug interaction study with oral hormonal contraceptive for ritlecitinib 200 mg QD (B7981018) and 50 mg ritlecitinib 50 mg QD (B7981035), a palatability study which investigated the palatability of oral formulations of ritlecitinib for pediatric use (B7981021), a relative bioavailability study of candidate capsule formulations of ritlecitinib relative to tablets (B7981022), a drug interaction study with itraconazole (B7981023), a drug interaction study with rosuvastatin (B7981024), a drug interaction study with sumatriptan (B7981025), a drug interaction study with rifampin (B7981026), and a PK study in Chinese participants (B7981036). Ritlecitinib was also investigated in specific populations of hepatic impairment (B7981016) and renal impairment (B7981020). Ritlecitinib has been investigated in 2 Phase 2 trials in participants with RA (B7981006) and AA (B7981005). There are ongoing studies in participants with AA (B7981015 and B7981032), Vitiligo (B7981019), UC (B7981005) and CD (B7981007).

2.2.4.2. PK Overview of Ritlecitinib

The PK profile of ritlecitinib is characterized by rapid absorption (T_{max} of ~1 hour), rapid elimination ($t_{½}$ of ~2 hours) and is approximately dose proportional. 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. Even though ritlecitinib has a short $t_{½}$ (~2 hours), 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 (pre-dose) ritlecitinib beyond Day 6. The accumulation ratio for 50 and 200 mg QD was also 1.4 and 1.8 respectively, suggesting nonlinear characteristics of ritlecitinib PK. Ritlecitinib is primarily cleared by metabolism. Less than 8% of ritlecitinib is excreted unchanged in the urine.

2.2.4.2.1. Studies in Healthy Participants

In all 14 Phase 1 studies in healthy participants, ritlecitinib was found to be well tolerated and to have an acceptable safety profile.

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

2.2.4.2.2. Phase 2a Study in Rheumatoid Arthritis

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 200 mg QD. Participants remained on stable background arthritis therapy, which had to include methotrexate (supplemented with folic/folinic acid per the local treatment guidelines).

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. The majority 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, 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), lymphocyte counts (21% change from baseline), neutrophil counts (24% change from baseline), and hemoglobin (3% change from baseline). 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.

2.2.4.2.3. Phase 2a Study in Alopecia Areata

Study B7931005 is a Phase 2a, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety profile of ritlecitinib and PF-06700841 (a TYK2/JAK1 inhibitor) in participants with moderate to severe AA. The study consists of the initial

24-week double-blind treatment period, an up to 12-month single-blind extension period, and a 6-month 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.

During the initial 24-week double-blind treatment period, participants in the ritlecitinib group were treated with 200 mg of ritlecitinib 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 B7931005, there were no deaths and no participants in the ritlecitinib treatment group experienced an SAE. The proportion of participants who experienced TEAEs in the placebo treatment group (74.5%) was comparable with the ritlecitinib treatment group (62.5%). The TEAEs reported in more than 5% (1 in 20) participants with AA 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 change from baseline, 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. Neutrophil counts were increased at Week 4 (12% change from baseline) and Week 24 (10% change from baseline) in the ritlecitinib treatment group. Two participants in the ritlecitinib group discontinued due to TEAEs.

In addition to the initial 24-week period, the trial included 2 extensions. Extension 1 was a Single-Blind Extension Period in which the participants had treatment withdrawn and were then re-treated for up to 24 weeks with the initially assigned IP after the participants reached a pre-specified retreatment criterion (ie, 30% hair loss from the regrown hair at Week 24). The second extension was a Cross-Over Open Label Extension Period in which the Week 24 non-responders were assigned the opposite active treatment than the one received in the initial (Week 0-24) treatment period. There were no SUSARS, serious infections, adverse events of QTcF prolongation, malignancies and/or no case of herpes zoster during the extension periods.

More detailed information about ritlecitinib can be found in the current version of the ritlecitinib IB, which is the SRSD for this study.

2.3. Benefit/Risk Assessment

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

The SRSD for tolbutamide is the USPI for Tolbutamide[4]. The main potential side effect of tolbutamide is hypoglycemia. Treatment of subjects with 6-phosphate dehydrogenase (G6PD) deficiency can result in hemolytic anemia. Mild adverse reactions include gastro-intestinal effects (nausea, epigastric fullness, heartburn). AEs due to dermatologic, hematologic, metabolic and endocrine reactions can occur as described in the USPI.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: Ritlecitinib		
Reductions in platelet counts and lymphocyte counts.	In B7931005 study, reductions in platelet counts and lymphocyte counts were observed during treatment with 200 mg QD but were not considered clinically meaningful and improved after switching to 50 mg QD.	Eligibility criteria and study assessments have been selected to ensure that only appropriate participants are included in the study.
Potential risk of infections.	Ritlecitinib is an immunomodulator and, as such, can be associated with the potential risk of infections (including serious infections), opportunistic infections, and viral reactivation.	Participants with significant infection history will be excluded (See Section 5.2) and the occurrence of infections will be monitored in the study.
Potential fetal risk.	In animals, ritlecitinib was associated with fetal changes in bones and some internal organs, and lower fetal body weights.	WOCBP who are unwilling or unable to use contraception as defined in the study protocol will be excluded (See Section 5.3.4. and Appendix 4).
Potential risk of secreting into human milk.	It is not known whether ritlecitinib is secreted into human milk.	Ritlecitinib should not be administered to breastfeeding women and exposure during breastfeeding should be reported to Pfizer Safety (See Section 8.3.5.2).
Study Intervention: Tolbutamide		
Phototoxicity	Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.[5]	The risk of phototoxicity with a single dose of tolbutamide (500 mg) is considered to be low. Additionally, participants will remain at the clinic during study participation and will be monitored.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Hypoglycemia	Tolbutamide is an oral blood glucose lowering drug of the sulfonylurea category. As with all sulfonylurea medications, there is a potential risk of hypoglycemia in patients with renal/hepatic/adrenal/pituitary insufficiency. Elderly, debilitated, malnourished patients or those taking beta-adrenergic blocking drugs may be at increased risk of hypoglycemic episodes. Severe/prolonged exercise and alcohol use may also increase the risk of hypoglycemia.	The risk of clinically significant hypoglycemia with a single dose of tolbutamide (500 mg) is considered to be low. In addition, the study will enroll healthy volunteers and exclude subjects with metabolic conditions that would increase their risk of participation. Subjects will remain at the clinic during study participation; physical activity, nutrition, and laboratory results will be monitored.
Gastrointestinal, dermatological, hematological, metabolic, and endocrine reactions.	Potential adverse reactions associated with tolbutamide or sulfonylurea treatment.[5]	A single dose of tolbutamide (500 mg) will be administered as part of the B7981069 and the risk of associated adverse reactions or laboratory abnormalities is low. Laboratory results and signs/symptoms will be monitored.

2.3.2. Benefit Assessment

Neither ritlecitinib nor tolbutamide is expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate PK, safety, and tolerability data for further clinical development of ritlecitinib.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to study participants, the potential risks identified in association with ritlecitinib and tolbutamide are justified by the anticipated benefits that may be afforded to patients with AA, vitiligo, RA, UC and CD treated with ritlecitinib.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To evaluate the effect of multiple-dose ritlecitinib (PF-06651600) on the PK of a single, oral dose of tolbutamide in healthy participants.	• C_{max} and AUC_{inf} (if data permit, otherwise AUC_{last}) of tolbutamide.
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of ritlecitinib when coadministered with a single dose of tolbutamide.	• Incidence of treatment-emergent adverse events
Other/Exploratory:	**Other/Exploratory:**
• To characterize the PK of a single oral dose of tolbutamide in healthy participants.	• Plasma tolbutamide PK parameters:T_{max}, AUC_{last}, CL/F, V_z/F and $t_{½}$, as data permit.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, 2-period, multiple-dose, open-label, single fixed sequence study of the effect of ritlecitinib on tolbutamide pharmacokinetics in healthy participants. A total of approximately 12 healthy male and/or female participants will be enrolled in the study to obtain at least 10 evaluable participants who complete the study. Participants who withdraw from the study may be replaced at the discretion of the sponsor.

Participants will be screened within 28 days of the first dose of study medication. Participants will report to the CRU the day prior to Day 1 dosing (Day -1) in Period 1 for both treatment sequences. Participants will remain in the CRU for a total of 16 days and 15 nights. This includes 4 days and 4 nights (starting the night of admission to the CRU) in Period 1 and 12 days and 11 nights in Period 2. There will be no washout period between 2 treatment periods.

In Period 1, participants will be dosed with a single administration of tolbutamide 500 mg tablet on Day 1. Tolbutamide PK will be assessed for 36 hours following dosing. Period 1 will be immediately followed by Period 2 with no washout. In Period 2, participants will be dosed with oral 200 mg ritlecitinib QD for 10 days followed by administration of a single dose of 500 mg tolbutamide oral tablet within approximately 5 minutes after administration of a 200-mg dose of ritlecitinib on the morning of Day 10. Tolbutamide PK in Period 2 will again be assessed at pre-dose and over 36 hours after tolbutamide dosing. (Table 3)

Table 3. Treatment Flow Diagram

Period	Day*	Treatment
1	1	Tolbutamide 500 mg (single dose)
2	1-9	Ritlecitinib 200 mg QD
	10	Ritlecitinib 200 mg QD + tolbutamide 500 mg (single dose)
	11	No treatment given
	12	No treatment given (discharge)
Follow-up	28-35 after last dose of investigational product	Follow-up phone contact

*Note: Day is relative to the first day of study intervention dosing (including tolbutamide and ritlecitinib) in each period.

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.

4.2. Scientific Rationale for Study Design

The study is being designed as a fixed-sequence study to avoid the long washout period needed in a crossover design due to long half-lives of CYP enzymes to revert back to their baseline values. The fixed-sequence design has a low risk of period effect given the short time between the 2 periods. This is an open-label study not requiring an assessment of efficacy or pharmacodynamics markers, but it will include PK estimation for DDIs.

Since tolbutamide has a $t_{½}$ of 4.5 – 6.5 hours, plasma PK samples for tolbutamide will be collected up to 36 hours post-dosing to ensure that the majority of tolbutamide is recovered. There will be no separate washout between 2 periods, because 9 days of ritlecitinib dosing in Period 2 is considered adequate to cover the washout of tolbutamide from Period 1 based on ritlecitinib $t_{½}$.

4.2.1. Diversity of Study Population

Reasonable attempts will be made to enroll participants with other races than White and at least 1 female participant.

4.2.2. 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

4.3.1. Justification of Ritlecitinib Dose

The study will use the ritlecitinib dose of 200 mg given QD for 10 days. The choice of this dose is based on the highest ritlecitinib dose currently being evaluated in Phase 3 study for AA program. The dose level of 200 mg QD has demonstrated its safety and tolerability for up to 14 days in healthy participants (B7981001), up to 4 weeks in participants with AA (B7931005) and up to 8 weeks in RA participants (B7981006) (Refer to Section 2.2.4).

Enzyme induction can take several days for effects to manifest and alter enzyme activity. Multiple dose administration of the investigational drug for a minimum of 10 days is generally considered adequate. Therefore, ritlecitinib will be administered for 10 days in this study.

4.3.2. Justification of Tolbutamide Dose

The study will use the single dose of tolbutamide 500 mg. Tolbutamide is mainly metablized by CYP2C9 and acts as a sensitive substrate for this isoenzyme.[2,3] The therapeutic dose of tolbutamide is from 250 mg up to 3 g and most DDI studies involving tolbutamide as a substrate have been conducted at the 500 mg dose level.[2,6,7] In a drug interaction study with rifampin, a potent enzyme inducer for CP3A4, CYP2C19, CYP2C9, and CYP2B6, the total clearance of tolbutamide 500 mg SD was increased by about 1.92-fold.[7]

Tolbutamide is not known to induce or inhibit any metabolizing enzymes and therefore it is not expected to affect the exposures of ritlecitinib. Ritlecitinib is not expected to increase tolbutamide exposure. Thus, the combination of 200 mg ritlecitinib and 500 mg tolbutamide is expected to be generally safe and well tolerated by healthy participants.

4.4. End of Study Definition

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

A participant is considered to have completed the study if he/she has completed all periods of the study including the last scheduled procedure shown in the SoA.

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Male and female participants must be 18 to 65 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/or female participants who are healthy as determined by medical evaluation including medical history, full physical examination (including BP and pulse rate measurements), clinical laboratory tests, and 12-lead ECG.

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, dermatological 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. Known immunodeficiency disorder, including positive serology for HIV at screening, or a first degree relative with a hereditary immunodeficiency.

4. Infection with hepatitis B or hepatitis C viruses according to protocol specific testing algorithm.

    a. For hepatitis B, all participants will undergo testing for HBsAg and HBcAb. Only participants who are both HBsAg negative and HBcAb negative are eligible (regardless of the HBsAb result, if the latter is also reported due to local standard of care).

    b. For hepatitis C, all participants will undergo testing for HCVAb. Only participants who are HCVAb negative are eligible.

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

    - Any infection requiring treatment within 2 weeks prior to the dosing visit.
    - Any infection requiring hospitalization or 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 investigational product.
    - Known active or history of recurrent bacterial, viral, fungal, mycobacterial or other infections.
    - History of recurrent (more than one episode of) localized dermatomal herpes zoster, or history of disseminated (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 or symptoms suggestive of current lymphatic or lymphoid disease.

8. Known presence 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. Participants who, according to the product label for tolbutamide, would be at increased safety risk if dosed with tolbutamide.

10. History of hypersensitivity to tolbutamide or any of its excipients.

11. Other medical or psychiatric condition (including recent [within the past year] or active suicidal ideation/behavior, laboratory abnormality, or other conditions or situations related to COVID-19 pandemic [eg, contact with a 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 entry into this study.

12. Known glucose 6-phosphate dehydrogenase (G6PD) deficiency.

Prior/Concomitant Therapy:

13. Use of prescription or nonprescription drugs and dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to Day 1. Limited use of nonprescription medications that are not thought 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.

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

14. Systemic therapy with any of the medications that are moderate or strong CYP2C9 inhibitors within 28 days or 5 half-lives (whichever is longer) or moderate or strong CYP2C9 inducers within 28 days or 5 half-lives (whichever is longer) prior to the first dose of investigational product (Section 6.8).

15. Vaccination with a live attenuated vaccine within 6 weeks prior to the first dose of study intervention (refer to Section 5.3.5 for additional details).

Prior/Concurrent Clinical Study Experience:

16. Previous administration of investigational products (eg, drugs or vaccines) within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of investigational product used in this study (whichever is longer).

17. Known participation in a clinical trial of ritlecitinib and the participant experienced a ritlecitinib-related AE that led to discontinuation or had a ritlecitinib-related SAE.

Diagnostic Assessments:

18. A positive urine drug test.

19. A positive pregnancy test.

20. 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.

21. Any of the following conditions:

    - Screening 12-lead ECG that demonstrates:

        - Clinically significant abnormalities requiring treatment (eg, acute myocardial infarction, serious tachy- or brady-arrhythmias) or indicating serious underlying heart disease (eg, cardiomyopathy, Wolff Parkinson–White syndrome);

        - Confirmed QTcF (time from the start of the Q wave to the end of the T wave on ECG corrected using Fridericia's correction factor) prolongation (>450 milliseconds).

    - Long QT Syndrome, a family history of Long QT Syndrome, or a history of Torsades de Pointes;

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

    - AST or ALT level >1.5 × ULN;

    - Total bilirubin level >1.5 × ULN;

    - Hemoglobin level ≤120 g/L (12.0 g/dL);

    - Platelet count ≤150 × 10^9/L (150,000 cells/mm^3);

    - WBC count of ≤3.0 × 10^9/L (3000 cells/mm^3);

    - ANC <1500 cells/mm^3;

    - ALC <800 cells/mm^3;

    - eGFR <60 mL/min/1.73 m^2 based on the CKD-EPI equation;

    - In the opinion of the investigator or Pfizer (or designee), have any clinically significant laboratory abnormality that could affect interpretation of study data or the participant's participation in the study.

23. Have evidence of untreated or inadequately treated active or latent infection with Mycobacterium tuberculosis (TB) as follows (see details in Appendix 2).

    - A positive QFT-G In-Tube test performed within the 3 months prior to screening. If the laboratory reports the test result 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 In-Tube test only with approval from the Pfizer Medical Monitor on a case by case basis.

      Note: 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 multi drug resistant TB infection are <5% or an acceptable alternative regimen) or active (acceptable multi drug regimen) TB infection, neither a QFT-G In-Tube test nor a PPD test need be obtained.

      A participant who is being treated for latent or active TB infection is not eligible for this study.

Other Exclusions:

24. 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 (males) and 4 (females) 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).

25. Use of tobacco/nicotine containing products in excess of 5 cigarettes/day.

26. History of severe allergic or anaphylactic reaction to kinase inhibitors or excipients (if known, document the specific excipient or drug).

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

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

29. 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 12 hours prior to any safety laboratory evaluations.

- Noncaffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices, see below) may be consumed with meals and the evening snack.

- On PK days (Period 1 Day 1 and Period 2 Day 10), participants should begin breakfast approximately 30 minutes prior to tolbutamide administration. The breakfast will be consumed over approximately a 20-minute interval with tolbutamide administered within approximately 10 minutes of completion of the meal. Participants will be encouraged to complete the entire breakfast. There are no water restrictions prior to and after dosing. No restriction will be placed on breakfast on other study days provided other restrictions are followed.

- On PK days (Period 1 Day 1 and Period 2 Day 10), lunch will be provided approximately 4 hours after tolbutamide dosing. Food restrictions only apply on the days when tolbutamide is dosed.

- On PK days (Period 1 Day 1 and Period 2 Day 10), dinner will be provided approximately 9 to 10 hours after tolbutamide dosing. Food restrictions only apply on the days when tolbutamide is dosed.

- An evening snack is 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 investigational product 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 alcohol for 24 hours prior (or as specified above for red wine) to admission to the CRU and during confinement in the CRU. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

- Participants will abstain from caffeine containing products for 24 hours prior to the start of dosing and during confinement in the CRU.

- 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 from the permitted list of contraception methods (see Appendix 4 Section 10.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception) considering that their risk for pregnancy may have changed since the last visit. In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.3.5. Vaccination

Vaccination with a live attenuated vaccine 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 attenuated vaccines 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 live attenuated 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).

Vaccines (including COVID-19 vaccines) that are not live attenuated are permitted.

5.4. Screen Failures

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

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, the term investigational product may be used synonymously with study intervention.

6.1. Study Intervention(s) Administered

For this study, the investigational products are ritlecitinib (PF-06651600, 200 mg provided as four 50 mg capsules) and tolbutamide (500 mg provided as one 500 mg tablet).

Ritlecitinib (PF-06651600) 50 mg capsules will be supplied to the CRU in bulk along with individual dosing containers for unit dosing.

Tolbutamide 500 mg tablets will be supplied to the CRU.

6.1.1. Administration

Administration of investigational product (ritlecitinib [PF-06651600] and/or tolbutamide) will be carried out according to the conditions described in the SoA and Section 5.3.1 of this protocol.

For Period 1, on Day 1, approximately 10 min after a standard breakfast, participants will receive tolbutamide at approximately 08:00 hours (±3 hours) with approximately 240 mL of ambient temperature water.

For Period 2, ritlecitinib will be administered under non-fasting conditions on Days 1 to 9. On the morning of Day 10, approximately 10 min after a standard breakfast, ritlecitinib and tolbutamide doses will be administered at 08:00 hours (±2 hours), with ambient temperature water to a total volume of approximately 240 mL. Ritlecitinib will be administered first. After swallowing the ritlecitinib dose, tolbutamide should be administered within approximately 5 minutes.

For coadministration day, participants may receive additional ambient temperature water up to 100 mL, if needed.

The time of ritlecitinib and tolbutamide administrations will be recorded.

Participants will swallow the investigational product whole, and will not manipulate or chew the investigational product prior to swallowing.

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

6.2. Preparation/Handling/Storage/Accountability

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

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

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the PCRU site procedures.

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

5. Study interventions should be stored in their original containers and in accordance with documentation provided to the site.

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 by CRU or as per local 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.

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.

Ritlecitinib (200 mg, four 50 mg capsules) and tolbutamide (500 mg, provided as one 500 mg tablet) 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 tablets and 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.

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

6.4. Study Intervention Compliance

Participants will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff. The oral cavity of each participant will be examined following dosing to ensure the investigational product was taken.

6.5. Dose Modification

Dose modification is not allowed in the current study.

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

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

6.7. Treatment of Overdose

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

Any dose of tolbutamide greater than 3000 mg within a 24-hour time period will be considered an overdose.

There is no specific antidote or specific treatment for an overdose of ritlecitinib. For tolbutamide, investigators should consider the treatment of overdose as per USPI.[5]

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities until ritlecitinib and tolbutamide can no longer be detected systemically (at least 2 days).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE.**
5. Obtain a blood sample for PK analysis within 4 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

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

6.8. Concomitant Therapy

Use of prescription or nonprescription drugs and dietary and herbal supplements are prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor. Acetaminophen/paracetamol may be used at doses of ≤3 g/day. Ibuprofen may be used at doses ≤1200 mg/day.

Systemic therapy with any of the medications that are moderate or strong CYP2C9 inhibitors or moderate or strong CYP2C9 inducers within 28 days or 5 half-lives (whichever is longer) are prohibited prior to the first dose of investigational product.

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

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

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

6.8.1. Rescue Medicine

There is no specific rescue therapy to reverse the AEs caused by ritlecitinib or tolbutamide; standard medical supportive care must be provided to manage the AEs.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following as outlined in Section 10.8.2.

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

See Appendix 8 for guidelines for safety monitoring and discontinuation guidelines.

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 follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;

- At the discretion of the investigator for behavioral, compliance, or administrative reasons.

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

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

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

If a participant withdraws from the study, he/she may request destruction of any remaining samples 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.

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

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 and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

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

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

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 group may be used in a subsequent 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 145 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

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, gastrointestinal including lymph nodes, skin and participant reported symptoms.

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

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

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

8.2.2. Vital Signs

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

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

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

8.2.2.1. Temperature

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

8.2.3. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10 second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) is not recommended 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 10 minutes in a supine position.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements (Period 1, Day 1 pre-dose). Additional ECG

monitoring will occur if a) a postdose QTcF interval is increased by ≥60 msec from the baseline **and** is >450 msec; or b) an 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 postdose 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 QTc intervals do not return to less than the criterion listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

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

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

8.2.4. Clinical Safety Laboratory Assessments

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

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

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

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

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

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

8.2.5. COVID-19 specific assessments

Participants will be tested for SARS-COVID-19 infection by PCR prior to being admitted to the clinic for confinement and a subsequent COVID-19 test will be performed after 4 days (i.e. upon completion of 4 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. Estimated Glomerular Filtration Rate

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

CKD-EPI

- If female and SCr is ≤0.7 mg/dL:

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

- If female and SCr is >0.7 mg/dL:

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

- If male and SCr is ≤0.9 mg/dL:

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

- If male and SCr is >0.9 mg/dL:

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

8.2.7. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ ECs or if required by local regulations.

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

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

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

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

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

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

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

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

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

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

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

Investigators are not obligated to actively seek information on AE or SAE after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she

considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

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

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, 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 are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.

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, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form,

regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

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

8.3.5.2. Exposure During Breastfeeding

An 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 inhalation or skin contact.

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 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 does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events (Not applicable)

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

8.3.8. Adverse Events of Special Interest (Not applicable)

8.3.8.1. Lack of Efficacy (Not applicable)

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

Blood samples of approximately 3 mL, to provide approximately 1 mL plasma, will be collected for measurement of plasma concentrations of tolbutamide as 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 (eg, within 6 minutes of a 60-minute sample) 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 data collection tool (eg, CRF/DCT). 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 data collection tool (eg, CRF/DCT).

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

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

Samples collected for measurement of plasma concentrations of tolbutamide 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.

8.5. Genetics

8.5.1. Specified Genetics

A 4-mL blood pharmacogenomic sample for DNA isolation will be collected into plastic K2-EDTA tubes, as defined in the SoA. DNA samples will be analyzed for the purpose of assessing the impact of allelic variants of CYP2C9 as variation in this gene may influence the metabolism and PK of tolbutamide. Additionally, these samples may also be used for retrospective evaluation of additional genetic variants associated with variation in PK, biomarker response, or to explore AEs should these be observed. Samples will be retained for a period of up to 3 years after regulatory approval.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in sponsor-identified study-specific central laboratory manual. The PGx sample must be processed and shipped as indicated in the instructions provided to the investigator site, to maintain sample integrity. Any deviations

from the PGx processing steps, 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. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

Any data outside of the CYP2C9 genotyping will be used for internal exploratory purposes and will not be included in the clinical study report.

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.

Retained Research Samples may be used for research related to the study intervention(s) and safety biomarkers. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples.

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

Collection of samples for biomarker research is also part of this study.

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

- A 10 mL whole blood for serum (Prep B2) sample.

8.6.1. Retained Research Samples for Biomarkers

These Retained Research Samples will be collected in this study:

A 10 mL whole blood for serum (Prep B2) sample will be collected according to the SoA, as local regulations and IRB/ECs allow.

Retained Research Samples may be used for research related to the study intervention(s) and safety biomarkers. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples.

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.

8.7. 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 statistical hypothesis will be tested in this study.

9.2. Analysis Sets

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

Participant Analysis Set	Description
PK Parameter Evaluable	The PK Evaluable population is defined as all participants treated who have at least 1 of the PK parameters of primary interest in at least 1 treatment period.
PK Concentration	The PK Concentration population is defined as all participants treated who have at least 1 concentration in at least 1 treatment period.
Safety	All participants assigned to the study intervention and who take at least 1 dose of the study intervention. Participants will be analyzed according to the intervention they actually received.

9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses. Table 4 shows the definition for the PK parameters.

Table 4. Plasma Pharmacokinetic Parameter Definitions

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration-time profile from time 0 to time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal rule

Table 4. Plasma Pharmacokinetic Parameter Definitions

Parameter	Definition	Method of Determination
AUC_{inf}	Area under the plasma concentration-time profile from time 0 extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis, and k_{el} is the terminal phase rate constant calculated by a linear regression through at least 3 data points in the terminal phase of the log-linear concentration-time curve
C_{max}	Maximum plasma concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
CL/F	Apparent clearance	$Dose/AUC_{inf}$
V_z/F	Apparent volume of distribution following oral administration	$V_z/F = Dose/(AUC_{inf}*k_{el})$
$t_{½}$	Terminal plasma elimination half-life	$Log_e(2)/k_{el}$, Only those data points judged to describe the terminal log-linear decline will be used in the regression

9.3.1. General Considerations

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.

9.3.2. Primary Endpoints

Natural log-transformed parameters AUC_{inf} (if data permit, otherwise AUC_{last}) and C_{max} of tolbutamide will be analyzed using a mixed effect model with treatment as a fixed effect and participant as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CI for the ratios. Tolbutamide administered alone will be the Reference treatment and tolbutamide co-administered with ritlecitinib will be the Test treatment.

Actual PK sampling times will be used in the derivation of PK parameters. The tolbutamide AUC_{inf}, AUC_{last} and C_{max} will be listed and summarized descriptively by treatment.

9.3.3. Other Endpoints

The tolbutamide T_{max}, AUC_{last}, CL/F, V_z/F and $t_{½}$, as data permit, will be listed and summarized descriptively by treatment. Plasma concentrations will be listed and summarized descriptively by treatment and nominal PK sampling time. Individual participant and summary profiles (mean and median plots) of the plasma concentration-time data will be plotted using actual and nominal times, respectively.

9.3.4. Other Safety Analyses

All safety analyses will be performed on the safety population.

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

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

9.3.5. Other Analyses

Pharmacogenomic or biomarker data from Retained Research Samples may be collected during or after 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, and/or supporting clinical development.

9.5. Sample Size Determination

The following table presents the width of 90% confidence interval for approximately n=12 and different estimated effects of ritlecitinib on the pharmacokinetics of a single, oral dose of tolbutamide**.**

Table 5. Estimated 90% CIs for Different Underlaying Effects

Parameter	**Estimated Effect** (100*Test/Reference)	90% CI LB	90% CI UB	**90% CI Width**
AUC_{inf}	70%	59.1%	82.9%	23.8%
	75%	63.3%	88.8%	25.5%
	80%	67.6%	94.7%	27.2%
	85%	71.8%	100.7%	28.9%
	90%	76.0%	106.6%	30.6%
	95%	80.2%	112.5%	32.3%
	100%	84.4%	118.4%	34.0%
	105%	88.7%	124.3%	35.7%

These calculations are based on the estimate of within-participant standard deviation of 0.20 for tolbutamide $\log_e AUC_{inf}$ as obtained from published studies.[8,9,10]

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 and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

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

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 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 ICH GCP guidelines that the investigator becomes aware of.

10.1.2. 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 the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

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

A copy of the ICD(s) must be provided to the participant.

10.1.3. 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 identification. 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.

10.1.4. Committees Structure

10.1.4.1. Data Monitoring Committee

This study will not use a DMC.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the 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 available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

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

10.1.6. Data Quality Assurance

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

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.

10.1.7. Source Documents

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

Data reported on the CRF or entered in the 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.

In this study, the CRF will serve as the source document. A document must be available at the investigative site that identifies those data that will be recorded on the CRF and for which the CRF will be the source document.

Definition of what constitutes source data can be found in the source document locator, which is maintained by the sponsor.

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

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

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

10.1.8. 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 CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

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

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

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

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

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after 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.

10.1.10. Sponsor’s Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the Investigators Site Master File.

To facilitate access to appropriately qualified medical personnel for studyrelated medical questions or problems, participants are provided with an Emergency Contact Card (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 6) will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Table 6. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry (fasting)	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs and %) Eosinophils (Abs and %) Monocytes (Abs and %) Basophils (Abs and %) Lymphocytes (Abs and %)	BUN/urea and creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Albumin Total protein Uric acid CK Total cholesterol HDL cholesterol LDL cholesterol (calculated) Triglycerides **Additional Assessments for Hy's Law:** AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin GGT PT/INR Total bile acids	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	• COVID-19 testing • FSH[b] • Pregnancy test (β-hCG)[d] • HBsAg[e] • HBcAb[e] • HCVAb[e] • HIVQuantiFERON®-TB Gold Test[e] • Urine drug screening[e] • eGFR-CKD-EPI[e] • Viral screen[f] **Testing as indicated** (reflex testing; refer to Section 10.8.1 and Section 10.8.2 for guidance/criteria)**:** • FACS-TBNK • Urine myoglobin Section 10.8.1.

Table 6. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry (fasting)	Urinalysis	Other

a. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
b. At Screening for confirmation of postmenopausal status only.
c. At Screening and Admission. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).
d. Serum β-hCG for female participants of childbearing potential according to Schedule of Activities.
e. Complete at screening. Previous testing for QuantiFERON®-TB Gold Test will be accepted if completed within 12 weeks prior to baseline. Otherwise should be completed at screening and results available prior to Day -1.
f. A serum sample will be collected at baseline and submitted to the central lab. The sample will be stored and analyzed at a later date only at the sponsor's request. In certain cases of suspected viral infection (eg, disseminated herpes zoster or varicella), the sponsor may request to analyze the sample to determine if the subject had exposure to that virus.

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.

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

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

10.3.1. Definition of AE

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

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms;
 	
  • Requires additional diagnostic testing or medical/surgical intervention;
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

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

10.3.2. Definition of SAE

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 detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

d. Results in persistent 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) which 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 important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs 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, and occupational exposure	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/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.

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

Assessment of Intensity

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

- Mild: 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/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/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the 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) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

No contraception methods are required for male participants in this study based on the following considerations:

- Ritlecitinib is not likely to transfer to a partner through semen at pharmacologically relevant blood levels.
- According to the tolbutamide USPI information[5], there is no requirement for male contraceptive use during treatment.

10.4.2. Female Participant Reproductive Inclusion Criteria

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

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

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described below during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any 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 and for at least 28 days after the last dose of study intervention. 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.
     - For women using HRT, FSH should be measured after an appropriate washout of HRT (at least 14 days after the last dose of HRT). HRT must be discontinued at least 28 days before the first dose of ingestigational product and for at least 28 days after the last dose of ritlecitinib.
   - A female whose menopausal status is in doubt will be required to use one of the allowed nonhormonal highly effective contraception methods.

10.4.4. Contraception Methods

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

Highly Effective Methods That Have Low User Dependency

1. Non-hormonal Intrauterine device (IUD).
2. Bilateral tubal occlusion or ligation.

3. Vasectomized partner.

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

Highly Effective Methods That Are User Dependent

1. 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 multistudy 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.

    - Samples for specified genetic analysis (see Section 8.5.1) will be stored for up to 3 years after regulatory approval or other 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 an “adaptor” 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 cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum 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 Adverse Events
• 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 Serious Adverse Events

• 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 torsades de pointes)).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

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

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

10.8. Appendix 8: Guidelines for Participant Safety Monitoring and Discontinuation

These guidelines for participant safety monitoring and discontinuation are to be applied to all participants in Study B7981069. Additional individual participant monitoring is at the discretion of the investigator and dependent on any perceived safety concerns. Unscheduled clinical labs may be obtained at any time during the study to assess such concerns, and a participant may be withdrawn at any time at the discretion of the investigator.

10.8.1. Participant Safety Monitoring

All potential treatment-related events of rash will be followed up until resolution or agreement with Pfizer.

In the case of a positive urine pregnancy test, the participant will have investigational product interrupted and a serum sample collected on the same day (or as soon as possible) and submitted to the laboratory for pregnancy testing.

The following laboratory abnormalities require re-testing until resolution or agreement with Pfizer:

Laboratory Variable	Laboratory Value	Re-testing Timeframe[c]
Hematology		
Absolute Neutrophil Count	<1000/mm^3 (<1.0 × 10^9/L)	24-48 hours
Hemoglobin	<10.0 g/dL (<6.21 mmol/L or <100 g/L) OR Decrease of ≥2.0 g/dL from baseline	24-48 hours
Platelet count	<100,000/mm^3 (<100.0 × 10^9/L)	24-48 hours
ALC[a]	<600/mm^3 (<0.6 × 10^9/L)	24-48 hours
Serum Chemistry		
CK[b]	>3 × ULN	24-48 hours
AST	See Appendix 6 for potential cases of drug-induced liver injury.	24-48 hours
ALT	See Appendix 6 for potential cases of drug-induced liver injury.	24-48 hours
TBili	See Appendix 6 for potential cases of drug-induced liver injury.	24-48 hours

a. Participants with ALC <500/mm^3 (0.5 × 10^9/L) will be reflex-tested for FACS-TBNK until the ALC resolves or stabilizes at a level acceptable to the investigator and sponsor.
b. In addition to re-testing creatinine kinase >3 × ULN, urine myoglobin will be performed as reflex testing for any participant with CK >10 × ULN.
c. Timeframe is based on the awareness of the abnormal results.

10.8.2. Participant Discontinuation Criteria

Treatment will be discontinued and the participant withdrawn from this study for:

Adverse Events:

- Serious infections, defined as any infection (viral, bacterial, and fungal) requiring parenteral antimicrobial therapy or hospitalization for treatment or meeting other criteria that require the infection to be classified as serious adverse event;
- Treatment-related SAEs;
- Other serious or severe AEs, at the discretion of the investigator or sponsor.

ECG Findings:

- Confirmed QTcF >500 milliseconds;
- Confirmed increase from baseline in QTcF of >60 milliseconds.

Laboratory Abnormalities:

- All the following laboratory abnormalities require discontinuation if they are confirmed by retest. Refer to the re-testing timeframes for laboratory abnormalities in Section 10.8.1.
  - ANC <750/mm^3 (<0.75 × 10^9/L);
  - Hemoglobin <9.0 g/dL (<5.59 mmol/L or <90 g/L) or a decrease of >30% from baseline (either criterion or both);
  - Platelet count <75,000/mm^3 (<75.0 × 10^9/L);
  - ALC <500/mm^3 (<0.5 × 10^9/L).

    NOTE: Participants with ALC <500/mm^3 (0.5 × 10^9/L) will be reflex tested for FACS-TBNK until the ALC resolves or stabilizes at a level acceptable to the investigator and sponsor.
  - Creatine kinase >10 × ULN.

    NOTE: In addition to re-testing creatinine kinase >3 × ULN, urine myoglobin will be performed as reflex testing for any participant with creatine kinase >10 × ULN.

- AST or ALT that meet ANY of the following:
  - >3 times ULN with at least one total bilirubin value >2 times ULN;
  - >3 times ULN accompanied by signs or symptoms consistent with hepatic injury (eg, new onset elevated PT/INR);
  - Two sequential AST or ALT elevations >5 times ULN, regardless of total bilirubin or accompanying signs or symptoms.

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

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	activity of daily living
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC_{24}	area under the plasma concentration-time profile from time 0 to time 24 hours.
AUC_{last}	area under the plasma concentration-time profile from time 0 to time of the last quantifiable concentration
AUC_{inf}	area under the plasma concentration-time profile from time 0 extrapolated to infinite time
AV	atrioventricular
β-hCG	beta-human chorionic gonadotropin
bpm	beats per minute
BA	bioavailability
BAEP	Brainstem auditory evoked potentials
BID	twice a day
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CD	Crohn's Disease
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{last}	last quantifiable concentration
CL/F	apparent clearance
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CO_2	carbon dioxide (bicarbonate)
COVID-19	Coronavirus disease
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
C-SSRS	Columbia-Suicide Severity Rating Scale

Abbreviation	Term
CYP	cytochrome
CSR	Clinical Study Report
CT	clinical trial
DCT	data collection tool
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
EBV	Epstein Barr Virus
EC	ethics committee
ECC	Emergency Contact Card
ECG	electrocardiogram
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
FACS-TBNK	fluorescence-activated cell sorting- T-,B- and NK-cells
FIH	first in human
FSH	follicle-stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
HCVAb	hepatitis C antibody
HDL	high-density lipoprotein
HepBcAb	hepatitis B core antibody
HepBsAb	hepatitis B surface antibody
HepBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation
IGRA	Interferon Gamma Release Assay
IL	interleukin
INR	international normalized ratio
IQMP	Integrated Quality Management Plan
IRB	Institutional Review Board

Abbreviation	Term
IUD	intrauterine device
IV	intravenous
LB	lower bound
LDL	low-density lipoprotein
LFT	liver function test
JAK	Janus kinase
k_{el}	first-order elimination rate constant
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MMR	measles, mumps, and rubella
NK	Natural Killer
NOAEL	no-observed-adverse-effect level
PCRU	Pfizer Clinical Research Unit
PGx	pharmacogenomics
PI	principal investigator
PPD	purified protein derivative
PK	pharmacokinetic(s)
PNS	peripheral nervous system
PR	the period that extends from the beginning of the P wave until the beginning of the QRS complex
PT	prothrombin time
PVCs	premature ventricular contractions
PXR	pregnane X receptor
QD	once daily
QT	time from the beginning of the QRS complex to the end of the T wave
QTc	corrected QT interval
QTcF	corrected QTc using (Fridericia method)
QTF-G	QuantiFERON-TB Gold
qual	qualitative
RA	rheumatoid arthritis
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCr	serum creatinine
SD	single dose
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$:	terminal half-life

Abbreviation	Term
TB	tuberculosis
TBili	total bilirubin
TEAE	treatment-emergent adverse event
TEC	TEC gene
THC	tetrahydrocannabinol
T_{max}	time to reach C_{max}
TYK	tyrosine kinase
UB	upper bound
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
Vz/F	apparent volume of distribution following oral administration
WBC	white blood cell
WOCBP	woman of childbearing potential

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