A PHASE 1, OPEN-LABEL STUDY IN HEALTHY PARTICIPANTS TO INVESTIGATE THE PHARMACOKINETICS OF RITLECITINIB FOLLOWING SINGLE ORAL ADMINISTRATION OF MODIFIED RELEASE FORMULATIONS UNDER FED AND FASTED CONDITIONS

Study Intervention Number:	PF-06651600
Study Intervention Name:	Ritlecitinib
US IND Number:	130983
EuCT Number:	2023-505603-23-00
ClinicalTrials.gov ID:	N/A
Pediatric Investigational Plan Number:	N/A
Protocol Number:	B7981086
Phase:	1
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title: A Study to Learn How Different Manufactured Products of the Study Medicine Called Ritlecitinib are Taken up Into the Blood in Healthy Adults When Taken on an Empty Stomach or When Taken With a Meal in Healthy Adults

Document History

Document	Version Date
Amendment 1	07 Nov 2023
Original protocol	19 Jun 2023

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

Protocol Amendment Summary of Changes Table

Amendment 1 (07 November 2023)

Overall Rationale for the Amendment:

Description of Change	Brief Rationale	Section # and Name
	Non-substantial Modification(s)	
IP manual term is changed to ***EDR and protocol*** and ***PCRU's local/site procedure***.	IP manual will not be used in the study.	Sections 6.1.1 and 6.2.
Tasso device validation has been deleted.	Tasso device will not be used in this study because of the AEs of the Tasso device reported in a recent clinical study.	Sections 1.1, 1.3, 2.3.1, 3, 4.1, 4.2, 8.5, and 9.3.2.1.
Estimated total blood sampling volume for individual participants is updated from 155 mL to 150 mL.	Tasso device has been deleted and therefore, total blood sampling volume was updated accordingly.	Section 8.1.
Additional physical exam is added at the end of each period.	The physical exam will be more frequently conducted, including at Day 3 of each period or at early termination.	Section 1.3.
Additional description to Table 2 was added such as the treatment names A; B & C are representative.	It will clarify the discrepancy between protocol and randomization code.	Sections 1.1 and 4.1.

Editorial and formatting changes and clarifications were made throughout the document.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1, Open-Label Study in Healthy Participants to Investigate the Pharmacokinetics of Ritlecitinib Following Single Oral Administration of Modified Release Formulations Under Fed and Fasted Conditions

Brief Title:
A Study to Learn How Different Manufactured Products of the Study Medicine Called Ritlecitinib are Taken up Into the Blood in Healthy Adults When Taken on an Empty Stomach or When Taken With a Meal in Healthy Adults.

Regulatory Agency Identification Number(s):

US IND Number:	130983
[EudraCT/EU CT] Number:	2023-505603-23-00.
ClinicalTrials.gov ID:	N/A
Pediatric Investigational Plan Number:	N/A
Protocol Number:	B7981086
Phase:	Phase 1

Rationale:

Ritlecitinib is a covalent and irreversible inhibitor of JAK3 with high selectivity over the other JAK isoforms (JAK1, JAK2, and TYK2). Ritlecitinib also inhibits irreversibly the 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, CD, AA, RA, and vitiligo and therefore under development in these indications. Moreover, 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.

This study aims to investigate the PK and relative bioavailability of 2 new MR capsule formulations of ritlecitinib, MR1 (release duration: 6-8 hours) and MR2 (release duration:13-15 hours) as single doses in fasted and fed conditions.

Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
• To determine the PK profile and relative bioavailability of ritlecitinib as 2 MR capsule formulations, MR1 and MR2, relative to solution formulation under fasted conditions in healthy adult participants.	• PK parameters of ritlecitinib (fasted): C_{max}, AUC_{inf} (if data permit), otherwise AUC_{last}
Secondary:	**Secondary:**
• To evaluate the effect of food on ritlecitinib exposure following administration as 2 MR capsule formulations, MR1 and MR2 in healthy adult participants.	• PK parameters of ritlecitinib (fed): C_{max}, AUC_{inf} (if data permit), otherwise AUC_{last}.
• To evaluate safety and tolerability of ritlecitinib following single oral administration as MR1 and MR2 capsule formulations in healthy adult participants.	• Assessment of AEs, clinical laboratory tests, vital signs and 12-lead ECG.

Overall Design

This is a single dose, open-label, randomized, 4-period, 6-sequence crossover study in a single cohort of approximately 12 healthy participants randomized to one of the sequences (containing 1 solution and 2 modified release [MR1 and MR2] capsule formulations of ritlecitinib) described in the table below where the treatment names A; B & C are representative. The first 3 periods are under fasted condition and the fourth period is under fed condition to investigate the effect of food on the PK of MR1 and MR2.

Study design and treatments

Sequence	Period 1	Period 2	Period 3	Period 4
1 (n=2)	A	B	C	B, fed
2 (n=2)	B	C	A	B, fed
3 (n=2)	C	A	B	B, fed
4 (n=2)	A	B	C	C, fed
5 (n=2)	B	C	A	C, fed
6 (n=2)	C	A	B	C, fed

Treatment A: ritlecitinib 100 mg PO solution
Treatment B: ritlecitinib 100 mg (2 × 50 mg) MR1 capsules
Treatment C: ritlecitinib 100 mg (2 × 50 mg) MR2 capsules

Number of Participants

A total of approximately 12 healthy male and/or female adult participants will be randomly assigned to study interventions in the study.

Study Population:

Key inclusion and exclusion criteria are listed below:

Inclusion Criteria

Participants must meet the following key inclusion criteria to be eligible for enrollment into the study:

- Participants aged 18 or older (or the minimal age of consent in accordance with location regulations) at screening.
- Male and female participants who are healthy as determined by medical evaluation including a detailed medical history, full physical examination (which includes BP and pulse rate measurement), clinical laboratory tests, and 12-lead ECG.
- BMI of 16 to 32 kg/m^2, and a total body weight >45 kg (99 lb).
- Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.
- Capable of giving signed informed consent.

Exclusion Criteria

Participants with any of the following characteristics/conditions will be excluded:

- Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease.
- Any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy).
- Known immunodeficiency disorder, including positive serology for HIV, or a first degree relative with a hereditary immunodeficiency.
- Infection with hepatitis B or hepatitis C viruses according to protocol specific testing algorithm history.
- Participants with any of the specified acute or chronic infections or infection history.
- History of febrile illness within 5 days prior to the first dose of study intervention.

- 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.

- Known present or a history of malignancy other than a successfully treated or excised nonmetastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.

Evidence of untreated or inadequately treated active or latent Mycobacterium TB infection.

Study Arms and Duration:

Study Interventions			
Intervention Name	ritlecitinib (100 mg) solution	ritlecitinib (100 mg) MR1	ritlecitinib (100 mg) MR2
Use	Experimental		
Dose Formulation	PO solution	Capsule	Capsule
Unit Dose Strength	100 mg in 100 mL provided in dosing bottle	50 mg/capsule	50 mg/capsule
Route of Administration	Oral		
IMP or NIMP/AxMP	IMP		

Study Interventions				
Study Interventions	**Period 1**	**Period 2**	**Period 3**	**Period 4**
Study Interventions Description	Participants will receive a single dose of IP on Day 1 of each period.			

For a given participant, the total study duration from screening to follow-up phone call will be between approximately 8 to 11 weeks.

Screening will occur within 28 days prior to the first dose of the study intervention. Each participant will go through Periods 1 through 4 and dosing in each treatment period will be separated by at least 3 days to minimize any carryover effect.

Venous PK blood samples for PK analysis will be collected pre-dose and at times specified in the SoA.

Participants may be discharged between periods at the discretion of PI. Following final discharge, participants will receive a follow-up phone call 28 to 35 days following the last dose of study intervention.

Participants who discontinue prior to completion of the study for reasons unrelated to safety may be replaced at the discretion of the PI and the sponsor. Participants withdrawn for safety reasons will not be replaced.

Statistical Methods

This study will include relative bioavailability and food effect evaluations. In the relative bioavailability evaluation, natural log transformed AUC_{inf} (if data permit), AUC_{last}, and C_{max} of ritlecitinib will be analyzed using a mixed effect model with treatment, sequence, and period as fixed effects and participant within sequence as a random effect. In the food effect evaluation, dose-normalized natural log transformed AUC_{last} and C_{max} of ritlecitinib will be analyzed using a mixed effect model with treatment and sequence as fixed effects and participant within sequence as a random effect. For both the relative bioavailability and food effect evaluation, estimates of the adjusted mean differences (Test/Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios.

The plasma concentrations of ritlecitinib will be listed and descriptively summarized by nominal PK sampling time, formulation and food condition. Ritlecitinib PK parameters will also be summarized by formulation and food condition. 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.

Ethical Considerations:

The results of previous studies of ritlecitinib support the investigation of ritlecitinib for AA, RA, vitiligo, UC and CD. Taking into account the measures to minimize risk to participants, the potential risks associated with ritlecitinib are justified by the anticipated benefits of informing safety and pharmacokinetics of MR formulations of ritlecitinib for future clinical development of therapies localized to the gut.

This is a short-term PK study and therefore no benefit to the participants is expected.

Based on the current clinical and nonclinical experience with ritlecitinib and information from other JAK inhibitors and TEC family kinase inhibitors (eg, tofacitinib, ruxolitinib, baricitinib, upadacitinib, abrocitinib, ibrutinib and acalabrutinib), the important potential risks for ritlecitinib are: serious infections, opportunistic infections and viral reactivation, malignancy, and thromboembolism. Identified risks that could have adverse outcomes include: dermatologic effects (ie. rash, urticaria), decreased lymphocyte counts, and decreased platelet counts.

Participants will be expected to commit time and may experience some discomfort while undergoing study assessments. In addition, participants of childbearing potential must agree to use appropriate contraception methods. Participants should avoid vaccination with live attenuated replication-competent vaccines. It is recommended that participants keep their diet habits constant throughout the study.

1.2. Schema

Not applicable.

1.3. Schedule of Activities

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

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

Visit Identifier Abbreviations used in this table may be found in **Appendix 9: Abbreviations**.	**Screening**	**Treatment Period**															**Notes**
		Period 1				**Period 2**			**Period 3**			**Period 4**			**Follow-up Contact**	**Early Termination/ Discontinuation**	• Follow-up contact will occur by telephone and must occur 28 to 35 days after the last administration of ritlecitinib.
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 1**	**Day 2**	**Day 3**	**Day 1**	**Day 2**	**Day 3**	**Day 1**	**Day 2**	**Day 3**	**28-35 Days after last dose in Period 4**		
Study Day	**-28 to -2**	-1	1	2	3	4	5	6	7	8	9	10	11	12			
Informed consent	X																
CRU confinement		X	→	→	→	→	→	→	→	→	→	→	→	X			• Period 4: final discharge from CRU. Participants may be discharged between periods at the discretion of PI.
Inclusion/exclusion criteria	X	X															• Inclusion/exclusion criteria should be updated on Day -1 since screening.

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Study Day	**-28 to -2**	-1	1	2	3	4	5	6	7	8	9	10	11	12			
Medical/medication history (update)	X	X															• Period 1 only. • Include history of alcohol abuse, tobacco/nicotine containing products, licit and illicit drug use or dependence within 6 months of Screening. For Day -1, records should be reviewed or updated only.

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Study Day	**-28 to -2**	-1	1	2	3	4	5	6	7	8	9	10	11	12			
Physical examination	X	X			X			X			X			X		X	• Complete (full) physical examination must either be conducted at Screening or upon Admission on Day -1 of Period 1 only; brief physical examination will be performed on Day 3 of each period or at early termination/discontinuation, and as needed per investigator discretion if there are findings during the previous examination, new/open adverse events.

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		Period 1				**Period 2**			**Period 3**			**Period 4**			**Follow-up Contact**	**Early Termination/ Discontinuation**	• Follow-up contact will occur by telephone and must occur 28 to 35 days after the last administration of ritlecitinib.
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Study Day	**-28 to -2**	-1	1	2	3	4	5	6	7	8	9	10	11	12			
Safety laboratory	X	X			X			X			X			X		X	• Participants should fast for at least 4 hours prior to any safety blood collection. Additional laboratory assessments may be performed if deemed necessary by the investigator. Refer to Table 5 in Section 10.2. Day 3 safety labs of every period to be done after PK blood sampling.
Demography, height and weight	X																

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Study Day	**-28 to -2**	-1	1	2	3	4	5	6	7	8	9	10	11	12			
Pregnancy test (WOCBP only)	X	X															• Given that the participant will be confined in CRU for the entire study, if tested negative on admission, no further test is needed.
Contraception check	X	X													X	X	• The contraception check is to confirm that contraception, if applicable, is used consistently and correctly.
Review prior or concomitant treatments and medications	X	X	→	→	→	→	→	→	→	→	→	→	→	→	X	X	
FSH (WONCBP only)	X																• Serum FSH for confirmation of postmenopausal status only
Urine drug testing	X	X															
Supine 12-lead single ECG	X		X			X			X			X		X		X	• Day 1 ECG to be done pre-dose.

Visit Identifier Abbreviations used in this table may be found in **Appendix 9: Abbreviations**.	**Screening**	**Treatment Period**														**Notes**
		Period 1				**Period 2**			**Period 3**			**Period 4**			**Follow-up Contact**	**Early Termination/ Discontinuation**	• Follow-up contact will occur by telephone and must occur 28 to 35 days after the last administration of ritlecitinib.
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Study Day	**-28 to -2**	-1	1	2	3	4	5	6	7	8	9	10	11	12			
Supine blood pressure, pulse rate and temperature	X		X			X			X			X		X		X	• Day 1 vital signs are collected prior to pre-dose (baseline) blood drawn.
HIV, HBsAg, HBcAb, HCVAb	X																• If HBsAg is negative and HBcAb is positive, HBsAb should be evaluated.
QuantiFERON®TB Gold test or equivalent	X																
Study intervention administration			X			X			X			X					• Please refer to Section 5.3.2 for details regarding dosing under fed and fasted state.
Pharmacokinetic blood sampling			X	X	X	X	X	X	X	X	X	X	X	X		X	• PK sample collection will be done pre-dose and at times post-dose as shown in Table 1 below.

Visit Identifier Abbreviations used in this table may be found in **Appendix 9: Abbreviations**.	**Screening**	**Treatment Period**															**Notes**
		Period 1				**Period 2**			**Period 3**			**Period 4**			**Follow-up Contact**	**Early Termination/ Discontinuation**	• Follow-up contact will occur by telephone and must occur 28 to 35 days after the last administration of ritlecitinib.
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Study Day	**-28 to -2**	-1	1	2	3	4	5	6	7	8	9	10	11	12			
Feces collection for MR2 (treatment C) arm only			X	X		X	X		X	X		X	X				• Each bowel movement to be collected only for the MR2 arm up to a period of 72 hours. Samples may be analyzed based on sponsor discretion.
Serious and nonserious adverse event monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X	
COVID-19 related procedures																	• Performed per local procedures

Table 1. Pharmacokinetic Sampling Schema for Each Period

Visit Identifier														**Notes**
Study Day	**1**										**2**		**3**	
Hours After Dose	**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**10**	**12**	**16**	**24**	**36**	**48**	• Hour 0 = predose PK samples collection. Any time prior to dosing ritlecitinib on the day of dosing.
Study intervention administration	X													
PK blood sampling for IR arm	X	X	X	X	X	X	X	X	X		X			• Ritlecitinib PK blood samples (2 mL blood to yield minimum of 0.5 mL plasma) are to be collected.
PK blood sampling for MR1 arm (fed and fasted)	X		X	X	X	X	X	X	X	X	X	X	X	
PK blood sampling for MR2 arm (fed and fasted)	X		X	X	X	X	X	X	X	X	X	X	X	

2. INTRODUCTION

Ritlecitinib is a selective covalent inhibitor of JAK3 and the 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 evaluate the PK, safety, and tolerability of ritlecitinib following single oral doses as IR and MR formulations in healthy, adult participants under fasted and fed conditions. The objective is to evaluate the relative bioavailability and food effect of 2 new MR capsule formulations, MR1 and MR2. Overall, results from this study will facilitate further development of an MR formulation for future clinical studies.

2.2. Background

Ritlecitinib is a covalent and irreversible inhibitor of JAK3 with high selectivity over the other 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, CD, AA, RA, and vitiligo. Moreover, 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.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

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

2.2.3. Nonclinical Safety

The NOAELs in the 6-month rat and second 9-month dog toxicity studies were 200 and 10 mg/kg/day, respectively. These exposures represent 50-fold exposure multiple in the rat study and a 7.4-fold exposure multiple in the dog study relative to the clinical dose of 50 mg. In the second 9-month dog toxicity study, the NOAEL of 10 mg/kg/day was based on adverse overimmunosuppression and axonal dystrophy (not axonal degeneration) in the CNS and the PNS at ≥20 mg/kg/day, accompanied by functional auditory deficits (BAEP) at the highest dose of 40 mg/kg/day (a 33-fold exposure multiple relative to the clinical dose of 50 mg).

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

2.2.4. Clinical Overview of Ritlecitinib

As of 30 May 2022, 26 clinical studies with ritlecitinib have been completed (22 Phase 1 studies in healthy participants or special populations and 6 Phase 2 or Phase 3 studies in participants with RA, AA, UC or vitiligo). A total of 464 participants were exposed to

ritlecitinib in the Phase 1 healthy participant and special population studies. In completed and ongoing interventional Phase 2 and Phase 3 studies in AA and vitiligo, 1628 participants have received ritlecitinib.

2.2.4.1. Pharmacokinetic Overview of Ritlecitinib

The PK profile of ritlecitinib is characterized by rapid absorption (following single doses of 5 to 200 mg, with median T_{max} values ≤0.75 hours; and more slowly at the higher doses, with a median Tmax of 1.00 and 1.50 hours for the 400- and 800-mg doses, respectively), rapid elimination ($t_{½}$ ranging from 1.1 to 2.5 hours) and are approximately dose proportional. Following multiple oral doses, steady-state was reached approximately by Day 4 due to non-stationary PK. Ritlecitinib has been evaluated at single oral doses ranging from 5 mg to 800 mg and multiple oral doses ranging from 50 mg to 400 mg QD and at 100 mg and 200 mg BID for 14 days. The clearance mechanisms for ritlecitinib in humans are primarily by metabolism, with approximately 4% of the dose excreted as unchanged drug in urine.

2.2.4.1.1. Effect of Food on PK of Ritlecitinib

Overall, food does not have a clinically significant impact on the systemic exposures of ritlecitinib and the product may be administered regardless of food intake.

In Study B7981003 (Module 5.3.1.1 B7981003 CSR), the co-administration of a single 50 mg tablet with a high-fat breakfast reduced C_{max} by ~39%, with no meaningful change in AUC_{inf} and a slight increase in T_{max}.

In Study B7981029 (Module 5.3.1.2 B7981029 CSR), the co-administration of a single 100 mg capsule with a high-fat breakfast reduced C_{max} by ~32% with no meaningful change in AUC_{inf} and a slight increase in T_{max}.

On the basis of the consistency of the PK results from B7981003 and B7981029 and dosing without regard to food in B7981015 Phase 2b/3 trial, ritlecitinib may be administered with or without food.

2.2.4.2. Safety Overview of Ritlecitinib

2.2.4.2.1. Studies in Healthy Participants

In 22 healthy participant studies, ritlecitinib was found to be well tolerated and to have an acceptable safety profile.

Additional single dose 2- or 3-way crossover studies were performed to examine drug interactions (B7981017, B7981018, B7981023), food effect and relative bioavailability (B7981003) of ritlecitinib. Each study included 12 to 14 healthy participants.

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

The current IB should be referred to for more detailed information.

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, multicenter 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 majority of the AEs were mild in severity. Overall, the most frequently reported treatment-related TEAE was Lymphopenia (2 [2.9%] participants in total: 2 [4.8%] participants in the ritlecitinib group and 0 participants in the placebo group). A total of 3 participants (7.1%) in the ritlecitinib group and 0 participants in the placebo group permanently discontinued due to TEAEs. One participant discontinued due to suicidal ideation, 1 participant discontinued due to lymphopenia, and the third participant discontinued due to hepatotoxicity. There were no SAEs nor deaths among participants who participated in Study B7981006.

2.2.4.2.3. Phase 2a Study in Crohn's disease

Study B7981007 is an ongoing Phase 2a, randomized, double-blind, placebo-controlled, parallel group, multicenter study to examine the efficacy of ritlecitinib (200 mg QD for 8 weeks followed by 50 mg QD for 4 weeks or placebo) and PF-06700841 in participants with moderate to severe active CD.

As of 30 May 2022, a total of 241 patients were evaluable for AEs, of whom 188 have reported 735 AEs. The most frequently reported (≥5%) all causality AEs were Crohn's disease (14.9%), SARS-CoV-2 test positive (10.8%), abdominal pain (9.1%), headache (7.1%), arthralgia (6.6% each), acne, fatigue, lymphopenia, and urinary tract infection (5.0% each).

As of 30 May 2022, a total of 69 SAEs in 54 participants have been reported. Eleven SAEs were reported pre-randomization in 11 participants.

During the open-label extension period, as of 30 May 2022, 13 SAEs were reported in 14 participants of which 3 SAEs were assessed as treatment-related by the investigator. The following SAEs were considered unrelated to ritlecitinib by the investigator: tonsillitis, Crohn's disease (5 events; exacerbation/flare of CD), female genital tract fistula, abdominal abscess, diarrhea hemorrhagic, clostridium difficile infection, vomiting, ileus, diarrhea, abdominal pain (2 events), anaemia, small intestinal obstruction, and lymphopenia. Except for 1 event of female genital tract fistula, all other events recovered/resolved.

Three SAEs were considered related to ritlecitinib by the investigator, which included Clostridium difficile infection, diarrhoea haemorrhagic, and lymphopenia.

2.2.4.2.4. Phase 2b Study in vitiligo

Study B7981019 is a completed Phase 2b, randomized, double-blind, parallel group, multicenter, placebo-controlled, dose ranging study to investigate different doses of ritlecitinib with a partial blinded extension period to evaluate the efficacy and safety of ritlecitinib in active non-segmental vitiligo.

In the 24-week double-blind DR Treatment Period, participants were randomized to 1 of 5 treatment groups (2 groups with a ritlecitinib induction dose of 200 mg QD or 100 mg QD for 4 weeks followed by maintenance dosing of 50 mg QD for 20 weeks, and 3 groups with 50 mg QD, 30 mg QD, and 10 mg QD ritlecitinib dosing for 24 weeks) or matching placebo. There were 6 groups with QD dosing in the Extension Period of 24 weeks: ritlecitinib induction dosing of 200 mg for 4 weeks followed by maintenance dosing of 50 mg for 20 weeks (open-label); 3 groups with induction dosing of 200 mg for 4 weeks followed by maintenance dosing of 50 mg for 20 weeks, 50 mg for 24 weeks, and 30 mg for 24 weeks (blinded); brepocitinib only (induction dosing of 60 mg for 4 weeks followed by maintenance dosing of 30 mg for 16 weeks [open-label]); observation-only (no treatment) group (open-label).

In the DR treatment period, of the 364 treated participants (298 treated with ritlecitinib), 66 (18.1%) discontinued from study intervention, of whom 11 received placebo treatment. Across treatment groups, the proportion of participants who discontinued study intervention ranged from 13.4% (100/50 mg) to 28.0% (30 mg). The primary reason for discontinuation from study intervention was withdrawal by participant (29 [8.0%]). There were 19 (5.2%) participants who discontinued study intervention due to AEs: 2 (3.1%) in 200/50 mg, 4 (6.0%) in 100/50 mg, 5 (7.5%) in 50 mg, 2 (4.0%) in 30 mg, 3 (6.1%) in 10 mg and 3 (4.5%) in placebo. In the Extension Period, there were 7 ritlecitinib treated participants who discontinued study intervention due to AEs.

The majority of all-causality TEAEs in participants across treatment groups in both treatment periods were mild or moderate in severity. There were 277 (76.1%) participants with 756 all causality TEAEs in the DR Period. The most frequently reported all-causality TEAEs were nasopharyngitis (15.9%), URTI (11.5%), and headache (8.8%). There were 126 (34.6%) participants with 195 treatment-related AEs. The most frequently reported treatment-related TEAEs were nasopharyngitis (4.1%), diarrhea (1.9%), and headache (1.9%). The majority of treatment-related TEAEs across treatment groups were mild or moderate in severity, and the number of severe events was not dose-dependent.

In the DR period, SAEs were reported in 4 participants (migraine in 50 mg, esophageal spasm in 30 mg, migraine in 10 mg, neurogenic bladder in placebo). All events were assessed as unrelated to the study intervention and the participants recovered. No SAEs were reported

in the 200/50 mg or 100/50 mg groups. One SAE (uterine leiomyoma, assessed as unrelated) was reported in the Extension Period.

There were no clinically meaningful trends for hematology, lipids, or chemistry lab parameters in participants treated with ritlecitinib.

2.2.4.2.5. Phase 2b/3 Study in Alopecia Areata

B7981015 was a Phase 2b/3, randomized, double-blind, placebo-controlled-, dose ranging- study to investigate ritlecitinib in participants with ≥50% scalp hair loss due to AA. The study had a maximum duration of approximately 57 weeks. This included an up to 5-week Screening period, a 48-week treatment period, and a 4-week follow-up period (for participants who did not roll over into the open-label, long-term Study B7981032). The treatment period was comprised of a placebo-controlled period that included a 4-week loading phase and a 20-week maintenance phase, followed by a 24-week extension phase. The study completed enrollment with a total of 718 participants. Eligible participants were randomized to blinded ritlecitinib and matching placebo in a 2:2:2:2:1:1:1 (200 mg/50 mg, 200 mg/30 mg, 50 mg, 30 mg, 10 mg, placebo-200 mg/50 mg, and placebo-50 mg, respectively) manner for a total of 7 treatment sequences.

A total of 1097 participants were screened and 718 participants were randomized to treatment. Of these, 715 (99.6%) received treatment (3 participants were not treated) and 101 (14.1%) discontinued treatment and 614 (85.5%) participants completed the study. The proportion of participants who experienced all-causality TEAEs was similar across treatment groups up to Week 24 (placebo-controlled period) and up to Week 48 (overall). Up to Week 24, the most frequently reported TEAEs in any group included nasopharyngitis, headache, and upper respiratory tract infection. The incidence of nasopharyngitis, folliculitis, urticaria, dizziness and urinary tract infection was higher in participants treated with ritlecitinib (particularly 200/50 mg and 200/30 mg) than placebo. Most TEAEs were mild to moderate in severity. Fourteen participants experienced 16 SAEs up to Week 48:

- 200/50 mg (4 participants): appendicitis; empyema and sepsis; invasive lobular breast carcinoma, spontaneous abortion.
- 200/30 mg (2 participants): appendicitis; chemical poisoning and suicidal behavior.
- 50 mg (2 participants): breast cancer; pulmonary embolism.
- 30 mg (1 participant): diverticulitis.
- 10 mg (2 participants): suicidal behavior; eczema.
- Placebo-200/50 mg: no SAEs.
- Placebo-50 mg (3 participants): spontaneous abortion; conversion disorder; heavy menstrual bleeding. These treatment-emergent SAEs were all reported during the Placebo Controlled Period.

Of the 16 SAEs, 12 were considered by the investigator as unrelated to study intervention. The 4 SAEs that were considered related to study intervention in the opinion of the investigator were sepsis and empyema (both in 1 participant); breast cancer; and eczema. There were no deaths in the study.
Treatment with ritlecitinib was associated with changes in hematological parameters, some of which were dose dependent. In the first weeks of the study, there were slight, transient decreases in hemoglobin and small, variable changes in neutrophil and leukocyte levels. Small, early decreases in platelets were observed with ritlecitinib treatment; these levels remained stable up to Week 48. Dose-dependent early decreases in absolute lymphocyte levels, T lymphocytes (CD3) and T lymphocyte subsets (CD4 and CD8) were observed. There was a dose-dependent early decrease in CD16/56 (NK cells), particularly in groups who had received a 200 mg loading dose of Ritlecitinib for 4 weeks. Overall, there were no clinically meaningful effects of ritlecitinib on ALT, AST, bilirubin, or alkaline phosphatase. The incidence of elevation in hepatic enzymes was low and not dose dependent. Up to Week 48, there were no potential Hy's law cases.

2.2.4.2.6. Phase 3 Study in Alopecia Areata

Study B7981032 is an ongoing 5-year Phase 3 open-label, multicenter study to evaluate the safety and efficacy of ritlecitinib in adult and adolescent participants ≥12 years of age with AA. The study has 2 treatment periods and an observation period with a maximum duration of approximately 38 months in the TP1. This phase includes up to a 5-week screening period, a 36-month open-label treatment period, and a 4-week follow-up period when not participating in the TP2. The TP2 is available for participants in countries where ritlecitinib is not commercially available at the time of their Month 36 visit. This includes up to 24 months of study intervention (or until availability of commercial product in their country, or until the sponsor terminates the study in that country, whichever occurs first) and a 4-week follow-up period after completion or discontinuation of the study intervention.
Study B7981032 includes eligible participants enrolling from the index Studies B7931005 and B7981015, as well as de novo participants (ie, those who have not previously received study intervention in Study B7931005 or B7981015).

As of 30 May 2022, a total of 1050 participants were evaluable for AEs, of whom 832 had reported 3369 TEAEs. The most frequently (≥5% of participants) reported TEAEs were SARS-CoV-2 test positive (17.8%), headache (14.3%), cough (7.9%), pyrexia (7.9%), and acne (7.7%). As of 30 May 2022, 56 (5.3%) participants were permanently discontinued from study intervention and/or the study due to a TEAE.

As of 30 May 2022, 45 participants had experienced 53 SAEs. There were 2 deaths reported in Study B7981032: a participant with breast cancer, and another with both acute respiratory failure and cardiorespiratory arrest.

The current IB should be referred to for more detailed information.

2.3. Benefit/Risk Assessment

Ritlecitinib is not expected to provide any clinical benefit to healthy participants of this study. Study B7981086 is designed to evaluate the performance of MR capsule formulations MR1 and MR2 of ritlecitinib under fasted and fed conditions. This study is designed primarily to generate safety, tolerability, and PK data for further clinical development of MR formulations of ritlecitinib. In this study, ritlecitinib will be administered at single doses of 100 mg.

Ritlecitinib was determined to be well tolerated and to have an acceptable safety profile in the clinical studies.

Based on clinical data (single oral doses of ritlecitinib up to 800 mg and multiple oral doses up to 400 mg), both 400 mg QD and 200 mg BID have demonstrated their safety and tolerability in healthy participants. The dose of 200 mg QD has demonstrated safety and tolerability of up to 8 weeks in RA patients (B7981006). In those studies, no clinically significant changes in vital signs, electrocardiogram or laboratory data were observed. No dose limiting AEs were reported and no participants met the protocol specified individual stopping rules. Hence, ritlecitinib is predicted to be well tolerated at a single dose of 100 mg in this study. In addition, participant safety is ensured by inpatient monitoring during the dosing period and throughout 48 hours postdose.

Ritlecitinib is an immunomodulator and, as such, can be associated with the potential risk of infections (including serious infections), opportunistic infections, and viral reactivation. The risk of infection will be monitored in this study.

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

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention ritlecitinib		
• viral reactivation • serious infections and opportunistic infections • malignancy and lymphoproliferative disorders • thromboembolism • dermatologic effects (eg, rash, acne, folliculitis, urticaria) • reduction in platelet count and lymphocyte count	Clinical experience with other JAK inhibitors Ritlecitinib clinical studies (B7931005, B7981015, B7981019, B7981032, and B7981037) and pre-clinical studies	Exclusion of participants at risk. Short duration of treatment. Safety labs at screening and baseline and when deemed necessary by the investigator throughout the study. AE monitoring throughout the study.
Study Procedures blood collection for PK		
Extravasation, bruising, local discomfort	Collection of up to 12 PK plasma samples per period per sequence	Use of highly qualified nurses, with venipuncture experience. Use of alternating arms for adjacent time points can provide more resting and healing time for each arm between samplings.

2.3.2. Benefit Assessment

There are no benefits to the participants in the study.

2.3.3. Overall Benefit/Risk Conclusion

Ritlecitinib will be administered for the first time as single dose of MR formulations MR1 and MR2 in healthy participants who would be contributing to the process of developing new and effective formulations to maximize the therapeutic index of therapies in any gastrointestinal indication. Medical evaluations/assessments associated with study procedures (eg, physical examination, ECG and labs) will be done for all participants in the study. There are no benefits to the participants and the risk to the participants is considered minimal.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To determine the PK profile and relative bioavailability of ritlecitinib as 2 MR capsule formulations, MR1 and MR2, relative to solution formulation under fasted conditions in healthy adult participants.	• PK parameters of ritlecitinib (fasted): C_{max}, AUC_{inf} (if data permit), otherwise AUC_{last}
Secondary:	**Secondary:**
• To evaluate the effect of food on ritlecitinib exposure following administration as 2 MR capsule formulations, MR1 and MR2 in healthy adult participants.	• PK parameters of ritlecitinib (fed): C_{max}, AUC_{inf} (if data permit), otherwise AUC_{last}.
• To evaluate safety and tolerability of ritlecitinib following single oral administration as MR1 and MR2 capsule formulations in healthy adult participants.	• Assessment of AEs, clinical laboratory tests, vital signs and 12-lead ECG.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To estimate additional PK parameters of ritlecitinib following single oral administration as MR1 and MR2 capsule formulations in healthy adult participants.	• T_{max}, and if data permit, T_{lag} , CL/F ,V_z/F , and $t_{½}$

4. STUDY DESIGN

4.1. Overall Design

This is a single dose, open-label randomized, 4-period, 6-sequence crossover study in a single cohort of approximately 12 healthy male and/or female participants randomized to one of the sequences (containing 1 solution and 2 MR [MR1 and MR2] capsule formulations of ritlecitinib) displayed in Table 2 where the treatment names A; B & C are representative. The first 3 periods are under fasted condition and the fourth period is under fed condition to

investigate food effect on the PK of modified release formulations MR1 and MR2. Dosing in each treatment period will be separated by at least 3 days to minimize any carryover effect. The study includes standard inpatient monitoring of study participants following single oral doses. Standard safety laboratory tests and urinalysis both before and after dosing will assess participant safety, while intensive blood draws following ritlecitinib administration will provide PK exposure data to characterize the relative bioavailability and absorption rate from different formulations. Normal venous PK blood samples for PK analysis will be collected pre-dose and at times specified in the SoA. For a given participant, the total study duration from screening to follow-up phone call will be between approximately 8 and 11 weeks. Participants may be discharged between periods at the discretion of PI.

Participants who discontinue prior to completion of the study for reasons unrelated to safety may be replaced at the discretion of the PI and the sponsor. Participants withdrawn for safety reasons will not be replaced.

Table 2. Study Design and Treatments

Sequence	Period 1	Period 2	Period 3	Period 4
1 (n=2)	A	B	C	B, fed
2 (n=2)	B	C	A	B, fed
3 (n=2)	C	A	B	B, fed
4 (n=2)	A	B	C	C, fed
5 (n=2)	B	C	A	C, fed
6 (n=2)	C	A	B	C, fed

Treatment A: ritlecitinib 100 mg PO solution
Treatment B: ritlecitinib 100 mg (2 × 50 mg) MR1 capsules
Treatment C: ritlecitinib 100 mg (2 × 50 mg) MR2 capsules

4.2. Scientific Rationale for Study Design

The current study aims to characterize PK and bioavailability of ritlecitinib as MR1 and MR2 formulations relative to solution formulation and to assess the food effect on the PK of MR1 and MR2 formulations in healthy participants.

The formulation of ritlecitinib that is currently being used in Phase 2 studies is a commercial IR capsule. In order to achieve more consistent delivery to the gut, 2 new MR capsule formulations (MR1, MR2) designed to deliver drug in a manner that is independent of the variability of GI transit times in fed and fasted conditions will be evaluated in this study.

In this study, MR1 and MR2, with in vitro release durations of 6-8 hours and 13-15 hours respectively, will be evaluated at a dose strength of 100 mg. Based on preliminary SimCYP simulations for these formulations, the sample collection up to 48 hours is deemed sufficient to characterize the concentration-time profile. In addition, a 3-day washout is expected to provide concentration <5% of C_{max} in the subsequent period for this study.

4.2.1. Choice of Contraception/Barrier Requirements

In animals, ritlecitinib was associated with fetal changes in bones and some internal organs, and lower fetal body weights. It is not known whether ritlecitinib is secreted into human

milk. Because of that and because of the investigational nature of ritlecitinib, it should not be administered to pregnant women, breastfeeding women, or fertile WOCBP who are unwilling or unable to use contraception as defined in the study protocol. Men in the study are not required to use birth control, because ritlecitinib is not likely to transfer to a partner through semen at pharmacologically relevant blood levels (see Appendix 4).

4.2.2. Collection of Retained Research Samples

Retained Research Samples will not be collected in this study.

4.3. Justification for Dose

A single dose of 100 mg is selected for MR capsules, MR1 and MR2. This dose, assuming 50% relative bioavailability, will result in systemic exposure equal to 50 mg IR which is a clinically relevant dose. A 100 mg PO solution will be used to establish relative bioavailability with this formulation and to support deconvolution to estimate regional absorption. The 100 mg dose has been used in other bioavailability studies for ritlecitinib (B7981022, B7981029).

Based on clinical data (single oral doses of ritlecitinib up to 800 mg and multiple oral doses up to 400 mg), both 400 mg QD and 200 mg BID have demonstrated their safety and tolerability in healthy participants. The dose of 200 mg QD has demonstrated safety and tolerability of up to 8 weeks in RA patients (B7981006). In those studies, no clinically significant changes in vital signs, electrocardiogram or laboratory data were observed. No dose limiting AEs were reported and no participants met the protocol specified individual stopping rules. Hence, ritlecitinib is predicted to be well tolerated at a single dose of 100 mg in this study. This dose is 8-fold lower than the highest single oral dose and 4-fold lower than the highest repeated oral dosing regimen evaluated in previous studies.

4.4. End of Study Definition

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

A participant is considered to have completed the study if they have 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, including participants across diverse and representative racial and ethnic backgrounds. If a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, race, and ethnicity. 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 aged 18 years or older (or the minimum age of consent in accordance with local regulations) at screening who are overtly healthy as determined by medical evaluation including medical history, physical examination, and laboratory tests.

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

Other Inclusion Criteria:

2. BMI of 16-32 kg/m^2, and a total body weight >45 kg (99 lb).

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

4. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1.3), 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:

5. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

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

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

   - 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.

- If HBsAg is positive, the participant must be excluded from participation in the study.
- If HBsAg and HBcAb are both negative, the participant is eligible for study inclusion.
- If HBsAg is negative and HBcAb is positive, HBsAb should be evaluated:

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

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

b. For hepatitis C, all participants will undergo testing for HCVAb. Participants who are HCVAb positive should be reflex-tested for HCV RNA and allowed to enroll only if negative.

6. Participants with any of the following acute or chronic infections or infection history:
   - Any infection requiring treatment within 2 weeks prior to dosing.
   - Any infection requiring hospitalization or parenteral antimicrobial therapy within 60 days of the first dose of study intervention.
   - Any infection judged to be an opportunistic infection or clinically significant by the investigator, within the past 6 months of the first dose of study intervention.
   - 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.
7. History of febrile illness within 5 days prior to the first dose of study intervention.
8. 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.
9. Known present or a history of malignancy other than a successfully treated or excised nonmetastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.

10. History of active or latent Mycobacterium TBA: participant who is currently being treated for active or latent Mycobacterium TB infection or has a history of Mycobacterium TB must be excluded from the study.

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

Prior/Concomitant Therapy:

12. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention with the exception of moderate/strong CYP3A inducers or inhibitors which are prohibited within 14 days plus 5 half-lives prior to the first dose of study intervention. (Refer to Section 6.9 Prior and Concomitant Therapy for additional details).

13. Vaccination with live attenuated replication-competent vaccine within the 6 weeks prior to the first dose of study intervention. (Refer to Section 5.3.5 for additional details).

Prior/Concurrent Clinical Study Experience:

14. Previous administration of an investigational product (drug or vaccine) within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer). Participation in studies of other investigational products (drug or vaccine) at any time during their participation in this study.

Diagnostic Assessments:

15. A positive urine drug test. A single repeat for positive drug screen may be allowed.

16. A positive serum pregnancy test.

17. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic) for participants <60 years; and ≥150/90 mm/Hg for participants ≥60 years old, following at least 5 minutes of supine rest. If systolic BP is ≥140 or 150 mm Hg (based on age) or diastolic ≥90 mm Hg, the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

18. Standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTcF >450 ms, complete LBBB, signs of an acute or indeterminate- age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third- degree AV

block, or serious bradyarrhythmias or tachyarrhythmias). If QTcF exceeds 450 ms, or QRS exceeds 120 ms, the ECG should be repeated twice, and the average of the 3 QTcF or QRS values should be used to determine the participant's eligibility. Computer interpreted- ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

19. Participants with **ANY** of the following abnormalities in clinical laboratory tests at screening or Day -1, as assessed by the study-specific- laboratory and confirmed by a single repeat test, if deemed necessary:

    - AST **or** ALT level > 1.5 × ULN;
    - Total bilirubin level >1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN;
    - Hemoglobin level <120 g/L (12.0 g/dL);
    - Platelet count $<150 \times 10^9$/L (150,000 cells/mm^3);
    - ANC $<1.2 \times 10^9$/L (1200 cells/mm^3);
    - ALC $<0.8 \times 10^9$/L (800 cells/mm^3);
    - eGFR <60 mL/minute/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.

Other Exclusion Criteria:

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

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

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

23. History of severe allergic or anaphylactic reactions.

24. WOCBP who are unwilling or unable to use an acceptable method of contraception as outlined in Section 10.4 during the intervention period and for at least 28 days after the last dose of study intervention.

25. Females on HRT and whose menopausal status is in doubt.

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

Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant and their partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. The investigator or designee will advise the participant to seek advice about the donation and cryopreservation of germ cells prior to the start of study intervention, if applicable.

At time points indicated in 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 and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

5.3.2. Meals and Dietary Restrictions

- Administration of investigational product will be done in fasted state in Periods 1-3 of this study, and under high-fat meal condition in Period 4.

- Under any meal condition, participants will refrain from consuming grapefruit, or grapefruit related- citrus fruits (eg, Seville oranges, pomelos) from 7 days prior to the first dose of study intervention until collection of the final PK blood sample.

- Except when the investigational product is dosed under high-fat meal condition, the total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein and the daily caloric intake per participant should not exceed approximately 3200 kcal while confined.

- The investigational product should be administered with approximately 240 mL of ambient temperature water.

- Lunch will be provided approximately 4 hours after dosing.

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

- An evening snack may be permitted.

Dosing under fasted condition:

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

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

Dosing under fed condition:

- Following an overnight fast of at least 10 hours (and collection of required laboratory and PK samples), participants should start a high fat (approximately 50% of total caloric content of the meal should be from fat; 30% from carbohydrates and 20% from protein – exceptions to this should be recorded), high calorie (approximately 800 to 1000 calories) breakfast approximately 30 minutes prior to administration of the investigational product. The breakfast will be consumed over approximately 20 minutes with investigational product administered within approximately 10 minutes after completion of the meal. Participants will be encouraged to eat the full meal on Day 1 and are required to eat a minimum of approximately 80% of the meal.

- The breakfast will be a high calorie/high fat test meal. The following breakfast as a representative example of a high fat, high calorie meal: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, 8 fluid ounces (240 mL) of whole milk.

- Water can be allowed as desired except for 1 hour after investigational product administration. There are no water restrictions prior to dosing for participants dosed under fed conditions.

5.3.3. Caffeine, Alcohol, and Tobacco

- Participants will abstain from caffeine containing products for 24 hours prior to the start of dosing until collection of the final PK sample of each study period.

- Participants will abstain from alcohol for 24 hours prior to admission to the CRU and continue abstaining from alcohol 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 the use of tobacco- or nicotine- containing products for 24 hours prior to dosing and during confinement in the CRU.

5.3.4. 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.

5.3.5. Vaccination

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

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

Recombinant subunit vaccines (eg, HepBV, HPV) are permitted and it is preferable that the last dose is administered at least 4 weeks prior to Day 1. Live attenuated vaccines that are known not to be replication-competent in humans are permitted. Such vaccines include but are not limited to the Modified Vaccinia Ankara Bavarian Nordic (Jynneos®, Imvamune®, Imvanex®) smallpox and monkeypox vaccine. By contrast, the ACAM2000 smallpox and monkeypox vaccine is prohibited because it is live and replicates in humans.

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

Individuals receiving immunosuppressive therapy may have a diminished response to vaccination.

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 study intervention/enrolled in the study. Screen failure data are collected and remain as source and are not reported on the CRF.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational and medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

For the purposes of this protocol, study intervention refers to ritlecitinib 100 mg dose.

6.1. Study Intervention(s) Administered

For this study, the study intervention is ritlecitinib, which will be administered as solution and MR1 and MR2 capsules.

Ritlecitinib as modified release formulations, MR1 and MR2, will be extemporaneously prepared by the CRU using bulk supply provided by Pfizer. Ritlecitinib PO solution dosages will similarly be extemporanously prepared by the CRU using materials provided by Pfizer.

Study intervention will be presented to the participants in individual dosing containers.

Table 3. Study Interventions

Intervention Name	ritlecitinib (100 mg) solution	ritlecitinib (100 mg) MR1	ritlecitinib (100 mg) MR2
Type	Small molecule		
Use	Experimental		
Dose Formulation	PO solution	Capsule	Capsule
Unit Dose Strength	100 mg in 100 mL provided in dosing bottle	50 mg/capsule	50 mg/capsule
Dosage Level	100 mg single dose	100 mg single dose	100 mg single dose
Route of Administration	Oral		
IMP or NIMP/AxMP	IMP		
Sourcing	Provided centrally by the sponsor.		
Packaging and Labeling	Extemporaneous preparation by the CRU	Extemporaneous preparation by the CRU	Extemporaneous preparation by the CRU

Study Interventions				
Study Interventions	**Period 1**	**Period 2**	**Period 3**	**Period 4**
	Experimental	Experimental	Experimental	Experimental
	Participants will receive a single dose of IP on Day 1 of each period.			

6.1.1. Administration

Investigational products will be administered orally and according to the conditions described in the Schedule of Activities and Meals and Dietary Restrictions of this protocol.

Following an overnight fast of at least 10 hours, participants will receive study intervention at approximately 0800 hours (plus or minus 2 hours). For fed period (Period 4), following an overnight fast of at least 10 hours, participants should start breakfast approximately 30 minutes prior to administration of the drug product. Investigator site personnel will administer study intervention during each period according to the EDR and Protocol with ambient temperature water to a total volume of approximately 240 mL. Participants will swallow the study intervention whole and will not manipulate or chew the study intervention prior to swallowing.

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

Administration of study intervention(s) at the site will be performed by an appropriately qualified and trained member of the study staff as allowed by local, state, and institutional guidance.

Following administration of study intervention(s) at the site, participants will be observed for 48 hours by an appropriately qualified and trained member of the study staff. Appropriate medication and other supportive measures for management of a medical emergency will be available in accordance with local guidelines and institutional guidelines.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm that appropriate conditions (eg, temperature) 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, prepare, and/or administer study intervention.

3. 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 upon return to business.

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to the labeled storage conditions, 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 excursion definition and information to report for each excursion will be provided to the site in the PCRU's local/site procedures.

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

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

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff 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.

8. Further guidance and information for the final disposition of unused study interventions are provided in the PCRU's local/site procedures. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the PCRU's local/site procedures.

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 MR1 and MR2 powder-in-capsules and Ritlecitinib oral solution will be prepared in the CRU by 2 operators, one of whom is a pharmacist. Details of dose preparation will be given in a separate EDR. Prepared doses will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the investigator site's labeling requirements.

6.3. Assignment to study intervention

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

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

6.4. Blinding

This is an open-label study.

6.4.1. Blinding of Participants

Participants will be unblinded to their assigned study intervention.

6.4.2. Blinding of Site Personnel

Investigators and other site staff will be unblinded to participants' assigned study intervention.

PCRU pharmacy staff responsible for preparing all study interventions will be unblinded. PCRU site staff providing technical system support to pharmacy staff and supporting blinded laboratory data processes will be unblinded. These site staff providing system support will not be involved in any data collection or clinic floor activities.

6.4.3. Blinding of the Sponsor

As this is an open label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, facilitating PK/PD modeling, and/or supporting clinical development.

6.5. Study Intervention Compliance

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

When participants are dosed at the site, they 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 other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.6. Dose Modification

Dose modification is not permitted during the study.

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

No study intervention will be provided to participants at the end of their study participation. It is expected that participants will be treated as required with standard-of-care treatments, as advised by their usual care physician.

6.8. Treatment of Overdose

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

There is no specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and follow up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). at least until the next scheduled follow-up.
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 study 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 study medical monitor as needed based on the clinical evaluation of the participant.

6.9. Prior and Concomitant Therapy

Participants will abstain from all concomitant treatments, except for the treatment of adverse events.

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 with the exception of moderate/strong CYP3A inducers or inhibitors which are prohibited within 14 days plus 5 half-lives- prior to the first dose of study intervention. Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case -by -case basis following approval by the sponsor. Acetaminophen/paracetamol may be used at doses of ≤1 g/day.

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

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

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

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: treatment-related SAEs, serious infections, and other events as described in Section 5.2.

Discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant should remain in the study to be evaluated for safety. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.1.1. Potential Cases of Acute Kidney Injury

Participants exposed to IMP demonstrating transient or sustained increase in Screat (with decrease in Screat-based eGFR or eCrCl) require expedited evaluation to differentiate AKI from DICI. DICI is defined as transporter-mediated effect related to altered renal tubular creatinine handling without histological injury.

AKI may be due to one or more types of injury, including DIKI. Differentiation of DIKI from other causes of AKI and from DICI may require clinical, radiographic, histopathologic, and laboratory assessments, as well as nephrology consultation.

Follow-up Assessments

The participant should return to the site for evaluation as soon as possible, preferably within 48 hours of awareness of the abnormal results.

Evaluation should include physical examination, laboratory tests, detailed medical and surgical history, review of all medications (including recreational drugs and supplements

[herbal]), family history, sexual history, travel history, blood transfusion, and potential occupational exposure to chemicals.

Laboratory assessments should include simultaneous serum cystatin C (Scys) and serum creatinine (Screat) tests. Estimates of eGFR, eCrCl and Screat-based eGFR and combined Screat-Scys-based eGFR should also be derived using the appropriate equation described in Appendix 7: Kidney Safety: Monitoring Guidelines.

Assessments of urine albumin-to-creatinine ratio or urine volume may also be performed as appropriate.

Differentiating Acute Kidney Injury from DICI

A confirmed Screat increase is defined as:
(i) ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours OR
(ii) confirmed Screat increase ≥1.5 times baseline (known or suspected to have occurred within the prior 7 days).

Based on the assessments performed, suspected AKI (including DIKI) may be differentiated from DICI as follows.

Adult participants

	AKI (including DIKI) **Any one of the below**	**DICI**
Scys & Screat	Simultaneous, confirmed serum cystatin C (Scys) increase and confirmed Screat increase	Confirmed Screat increase without confirmed increase in reflex Scys AND Confirmed Screat-based eGFR decrease without confirmed combined Screat-Scys-based eGFR decrease.
eGFR	Decrease in Screat-based eGFR and combined Screat-Scys-based eGFR (when available)	
Albuminuria or proteinuria	Confirmed albuminuria increase (see Appendix 7 for Grades A1 to A3 quantitation)	
Urine volume	Urine volume <0.5 mL/kg/h for 6 consecutive hours	

Regardless of the presence or absence of increase in Screat, DIKI and other causes of AKI may be suspected if either there is (i) new-onset or worsening albuminuria or proteinuria are detected or (ii) urine volume (if measured) is <0.5 mL/kg/h for 6 consecutive hours).

All confirmed cases of clinically relevant decrease in kidney function should be considered potential cases of DIKI if no other reason for the kidney function abnormalities has been found.

7.1.2. Liver Injury

A participant who meets the criteria as described in Appendix 6 will be withdrawn from study intervention.

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- Participant meeting protocol specified criteria for discontinuation.

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

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

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

If a participant withdraws from the study, they 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 will be performed and no additional data will be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol- specified follow- up procedures. The only

exception to this is when a participant specifically withdraws consent for any further contact with them 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 the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study;
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative 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.

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 because of unexpected delays (eg, delayed drug shipment), then participants do not require rescreening if the laboratory results obtained prior to first dose administration meet eligibility criteria.

A participant who qualified for this protocol but did not enroll from an earlier cohort/group may be used in a subsequent cohort/group without rescreening, provided laboratory results obtained prior to the first dose administration meet eligibility criteria for this study. In addition, other clinical assessments or specimen collections, eg, retained research samples, may not need to be repeated, 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 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 they have taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

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

The total blood sampling volume for individual participants in this study is approximately 150 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.

8.2. Efficacy Assessments

Efficacy parameters are not evaluated in this study.

8.3. Safety Assessments

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

8.3.1. Physical Examinations

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

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

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

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

Physical examination findings collected during the study will be considered source record 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 8.4.1 to 8.4.3.

8.3.2. Vital Signs

8.3.2.1. Blood Pressure and Pulse Rate

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.

Any untoward vital sign 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 8.4.1 to 8.4.3.

8.3.2.2. Temperature

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

8.3.3. Electrocardiograms

Standard 12-lead ECGs will be collected at times specified in the SoA section of this protocol using an ECG system that automatically calculates the HR and measures PR, QT, QTcF, and QRS intervals. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements, defined as pre-dose ECG of the current period. Additional ECG monitoring will occur if a) a postdose QTc interval is increased by ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QTc 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 ms from the baseline **and** is >450 ms; or b) an absolute QT value is ≥500 ms for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF value get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF values do not return to less than the criteria listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

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

ECG values of potential clinical concern are listed in Appendix 8.

8.3.4. 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 significant changes occurring during the study in the AE section of the CRF.

Clinically significant abnormal laboratory test findings are those that 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 significant and 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 study 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 DILI.

See Appendix 7 for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

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

8.3.5. COVID-19 Specific Assessments

Participants will be tested for COVID-19 prior to being admitted to the clinic for confinement), or if they develop COVID-19-like symptoms as required by local regulations or by the PI.

8.3.6. Pregnancy Testing

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

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

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

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally

authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc).

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

During the active collection period as described in Section 8.4.1, 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.

8.4.1. 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 undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days, except as indicated below, after the last administration of the study intervention.

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

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

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

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

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

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has concluded study participation, and they consider 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.

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 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 its being available.

8.4.1.2. 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 8.4.1, 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.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

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

8.4.2. 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.

8.4.3. Follow-Up of AEs and SAEs

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

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

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

8.4.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

Environmental exposure, occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

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

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention inseminates a female partner.
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion.

- A male family member or healthcare provider who has been exposed to the study intervention by ingestion then inseminates his female partner prior to or around the time of conception.

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

- If EDP occurs in a participant/participant's partner, the investigator must report this information to Pfizer Safety using the CT SAE Report Form and 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 at least 28 days after last dose of study intervention.

- 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 report 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 report. 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 pre-procedure 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 should be reported as an SAE;

- 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.

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

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

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

An EDB report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accordance with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the EDB.

8.4.5.3. Occupational Exposure

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

8.4.6. Cardiovascular and Death Events

Not applicable.

8.4.7. Disease Related- Events and/or Disease -Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.4.8. Adverse Events of Special Interest

GI disorders that include constipation, feces discoloration, diarrhea, dyspepsia, flatulence, nausea, vomiting, abdominal pain and occult blood will be reported as AEs of special interest to assess local tolerability of the MR formulations.

AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes. Should an aggregate analysis indicate that these prespecified events occur more frequently than expected, eg, based on epidemiological data, literature, or other data, then this will be submitted and reported in accordance with Pfizer's safety reporting requirements. Aggregate analyses of safety data will be performed on a regular basis per internal SOP.

All AESIs must be reported as an AE or SAE following the procedures described in Section 8.4.1 through Section 8.4.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.

8.4.8.1. Lack of Efficacy

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

8.4.9. Medical Device Deficiencies

Not applicable.

8.4.10. 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.

Medication errors are recorded and reported as follows:

Recorded on the Medication Error Page of the CRF	Recorded on the Adverse Event Page of the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	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.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, such medication errors occurring to a study participant are recorded on the medication error page of the CRF, which is a specific version of the AE page and, if applicable, any associated serious and nonserious AE(s), are recorded on the AE page of the CRF.

In the event of a medication dosing error, the sponsor should be notified within 24 hours. Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.5. Pharmacokinetics

Blood samples of approximately 2 mL, to provide a minimum of 0.5 mL of plasma, will be collected for measurement of plasma concentrations of ritlecitinib 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 relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

Samples will be used to evaluate the PK of study intervention. Samples collected for analyses of study intervention (plasma) concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes. The exploratory results may not be reported in the CSR.

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

Samples collected for measurement of plasma concentrations of study intervention 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.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.5.1. Feces collection and analysis

Feces will be collected for following oral administration of ritlecitinib (Treatment C only) up to 72 hours.

Details of the collection of aliquots, volume, processing, storage and shipping of the urine and feces samples will be provided in the lab manual and supporting documentation. The actual date and time (24-hour clock time) of each sample will be recorded. Samples may be analyzed at the discretion of the sponsor based on PK data from the study.

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.9. 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 the SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major

modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Hypotheses

No formal inferential statistics will be applied to the safety or PK data.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and randomization.
Full analysis set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.
Safety analysis set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.

Defined Analysis Set	Description
PK Concentration	The PK concentration population is defined as all participants randomized and treated who have at least 1 concentration in at least 1 treatment period.
PK Parameter	The PK parameter analysis population is defined as all participants randomized and treated who have at least 1 of the PK parameters of primary interest in at least 1 treatment period.

9.3. Statistical Analyses

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

9.3.1. General Considerations

Details of the analyses will be provided in the Statistical Analysis Plan. Briefly, ritlecitinib concentrations will be listed by participant and treatment, and summarized by treatment and food condition. Individual participant mean and median profiles of the plasma concentration-time data will be plotted by treatment and food condition using actual and nominal times, respectively. Mean and median profiles will be presented on both linear and log scales. Data permitting the PK parameters AUC_{last}, AUC_{inf}, C_{max}, T_{max}, and $t_{½}$ will be summarized by treatment and food condition as per Pfizer data standards.

For relative bioavailability analysis, the single dose of ritlecitinib MR1 and MR2 administered in fasted state are the Test treatments. Single dose of ritlecitinib solution under fasted condition is the Reference treatment. For food effect assessment, PF-06651600 MR1 and MR2 in fasted state are the Reference treatments while ritlecitinib MR1 and MR2 administered in fed state are Test treatments.

For the relative bioavailability evaluation, natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effect model with treatment, sequence, and period as fixed effects and participant within sequence as a random effect. For the food effect evaluation, natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effect model with sequence and treatment as fixed effects and participant within sequence as a random effect. In both analyses, estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios.

9.3.2. Pharmacokinetic analysis

Pharmacokinetic parameters following a single dose administration will be derived from the concentration-time profiles (actual PK sampling times will be used in the derivation of PK parameters) as follows in Table 4.

Table 4. Definitions of PK Parameters

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentrationtime profile from time 0 to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{inf}[a]	Area under the plasma concentration-time profile from time 0 extrapolated to infinite time	$AUC_{last} + (C_{last}/k_{el})$, where C_{last}[a] is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis
C_{max}	Maximum plasma concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{½}$[a]	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression
CL/F[a]	Apparent Clearance	$Dose/AUC_{inf}$
Vz/F[a]	Apparent volume of distribution after oral dose	$Dose/(AUC_{inf}*k_{el})$ after oral dose
T_{lag}[a]	Lag time	Time prior to the time corresponding to the first quantifiable concentration

a if data permits

9.3.3. 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.

9.3.3.1. Electrocardiogram Analyses

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

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

Safety QTc Assessment

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

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

9.3.4. Other Analyses

Pharmacogenomic or biomarker data from Banked Biospecimens 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 interim analysis will be conducted for this study.

9.5. Sample Size Determination

A sufficient number of participants will be screened to achieve 12 participants randomly assigned to study interventions such that exactly 2 participants will be enrolled to each of the 6 sequences. The sample size is empirically selected and is not based on statistical power calculation.

Analyses of data from studies B7981022, B7981029, and B7981030 suggest a within-participant standard deviation of 0.117 for log (AUC_{inf}) and within-participant standard deviation of 0.226 for log (C_{max}). The sample size of approximately 12 participants has been chosen.

The following table (Table 5) presents the reference boundaries and width of the confidence intervals for a range of estimates of the means ratio for pairs of treatments (Test vs Reference). The calculation assumes the selection of the default value (80%) of the tolerance parameter in the conventional calculation[1]. The values of within- participant standard

deviations (standard deviation of 0.117 for log (AUC_{inf}) and standard deviation of 0.226 for log (C_{max})) and corresponding widths of the confidence intervals were used. The width of the confidence intervals for fed versus fasted comparison is larger because only half of the participants contribute observations for this comparison.

Table 5. Expected Widths of the 90% Confidence Intervals (With 80% Tolerance Probability) for Different Possible Estimated Effects of ritlecitinib MR1 and MR2 Formulations in Fasted and Fed Conditions on PK Parameters

Estimated ratio of means	n=6				n=12				n=18			
	AUC_{inf}		C_{max}		AUC_{inf}		C_{max}		AUC_{inf}		C_{max}	
	90% CI	CI width	90% CI	CI width	90% CI	CI width	90% CI	CI width	90% CI	CI width	90% CI	CI width
MR/solution												
0.1	(0.08,0.12)	0.03	(0.07,0.14)	0.06	(0.09,0.11)	0.02	(0.08,0.12)	0.04	(0.09,0.11)	0.02	(0.09,0.12)	0.03
0.2	(0.17,0.24)	0.07	(0.15,0.27)	0.13	(0.18,0.22)	0.04	(0.17,0.24)	0.08	(0.19,0.22)	0.03	(0.17,0.23)	0.06
0.3	(0.25,0.35)	0.10	(0.22,0.41)	0.19	(0.27,0.33)	0.06	(0.25,0.36)	0.12	(0.28,0.32)	0.05	(0.26,0.35)	0.09
0.4	(0.34,0.47)	0.13	(0.29,0.55)	0.26	(0.36,0.44)	0.08	(0.33,0.48)	0.15	(0.37,0.43)	0.06	(0.35,0.46)	0.12
0.5	(0.42,0.59)	0.17	(0.36,0.69)	0.32	(0.45,0.55)	0.10	(0.41,0.61)	0.19	(0.46,0.54)	0.08	(0.43,0.58)	0.15
0.6	(0.51,0.71)	0.20	(0.44,0.82)	0.39	(0.54,0.66)	0.12	(0.50,0.73)	0.23	(0.56,0.65)	0.09	(0.52,0.70)	0.18
0.7	(0.59,0.83)	0.23	(0.51,0.96)	0.45	(0.63,0.77)	0.14	(0.58,0.85)	0.27	(0.65,0.76)	0.11	(0.60,0.81)	0.21
0.8	(0.68,0.94)	0.26	(0.58,1.10)	0.52	(0.72,0.88)	0.16	(0.66,0.97)	0.31	(0.74,0.86)	0.12	(0.69,0.93)	0.24
0.9	(0.76,1.06)	0.30	(0.66,1.24)	0.58	(0.82,0.99)	0.18	(0.74,1.09)	0.35	(0.83,0.97)	0.14	(0.78,1.04)	0.27
1	(0.85,1.18)	0.33	(0.73,1.37)	0.65	(0.91,1.10)	0.20	(0.83,1.21)	0.38	(0.93,1.08)	0.15	(0.86,1.16)	0.30
1.1	(0.93,1.30)	0.36	(0.80,1.51)	0.71	(1.00,1.21)	0.22	(0.91,1.33)	0.42	(1.02,1.19)	0.17	(0.95,1.28)	0.33
1.2	(1.02,1.41)	0.40	(0.87,1.65)	0.77	(1.09,1.32)	0.24	(0.99,1.45)	0.46	(1.11,1.30)	0.18	(1.04,1.39)	0.36
MR fed/fasted												
0.1	(0.07,0.14)	0.07	(0.05,0.20)	0.15	(0.08,0.12)	0.03	(0.07,0.14)	0.06	(0.09,0.11)	0.02	(0.08,0.13)	0.05
0.2	(0.14,0.28)	0.14	(0.10,0.40)	0.30	(0.17,0.24)	0.07	(0.15,0.27)	0.13	(0.18,0.23)	0.05	(0.16,0.25)	0.09
0.3	(0.21,0.43)	0.22	(0.15,0.59)	0.44	(0.25,0.35)	0.10	(0.22,0.41)	0.19	(0.27,0.34)	0.07	(0.24,0.38)	0.14
0.4	(0.28,0.57)	0.29	(0.20,0.79)	0.59	(0.34,0.47)	0.13	(0.29,0.55)	0.26	(0.35,0.45)	0.10	(0.32,0.50)	0.19
0.5	(0.35,0.71)	0.36	(0.25,0.99)	0.74	(0.42,0.59)	0.17	(0.36,0.69)	0.32	(0.44,0.56)	0.12	(0.40,0.63)	0.23
0.6	(0.42,0.85)	0.43	(0.30,1.19)	0.89	(0.51,0.71)	0.20	(0.44,0.82)	0.39	(0.53,0.68)	0.14	(0.48,0.76)	0.28
0.7	(0.49,1.00)	0.51	(0.35,1.39)	1.03	(0.59,0.83)	0.23	(0.51,0.96)	0.45	(0.62,0.79)	0.17	(0.55,0.88)	0.33
0.8	(0.56,1.14)	0.58	(0.40,1.58)	1.18	(0.68,0.94)	0.26	(0.58,1.1)	0.52	(0.71,0.90)	0.19	(0.63,1.01)	0.38

Table 5. Expected Widths of the 90% Confidence Intervals (With 80% Tolerance Probability) for Different Possible Estimated Effects of ritlecitinib MR1 and MR2 Formulations in Fasted and Fed Conditions on PK Parameters

Estimated ratio of means	n=6				n=12				n=18			
	AUC_{inf}		C_{max}		AUC_{inf}		C_{max}		AUC_{inf}		C_{max}	
	90% CI	CI width	90% CI	CI width	90% CI	CI width	90% CI	CI width	90% CI	CI width	90% CI	CI width
0.9	(0.63,1.28)	0.65	(0.45,1.78)	1.33	(0.76,1.06)	0.30	(0.66,1.24)	0.58	(0.80,1.02)	0.22	(0.71,1.14)	0.42
1	(0.70,1.42)	0.72	(0.50,1.98)	1.48	(0.85,1.18)	0.33	(0.73,1.37)	0.65	(0.89,1.13)	0.24	(0.79,1.26)	0.47
1.1	(0.77,1.57)	0.79	(0.56,2.18)	1.62	(0.93,1.30)	0.36	(0.80,1.51)	0.71	(0.98,1.24)	0.27	(0.87,1.39)	0.52
1.2	(0.84,1.71)	0.87	(0.61,2.38)	1.77	(1.02,1.41)	0.40	(0.87,1.65)	0.77	(1.06,1.35)	0.29	(0.95,1.51)	0.56

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

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

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

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP guidelines that the investigator becomes aware of.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or the investigator's 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 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 their 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 their 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 their right to access and correct their personal data and to withdraw consent for the processing of their personal data.

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

Participants must be reconsented to the most current version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

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

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

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow specimens to be used for additional research. Participants who decline to participate in this optional additional research will not provide this separate signature.

10.1.4. Data Protection

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

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

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participan-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 their actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use an E-DMC.

10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites 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/CTIS

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

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of “bona-fide scientific research” that contributes to the scientific understanding of

the disease, target, or compound class. Pfizer will make data from these trials available 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

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

10.1.7. Data Quality Assurance

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

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

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

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

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

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

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

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

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

10.1.8. Source Documents

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

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

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 a source document and its origin can be found in the Source Document Locator, which is maintained by the sponsor's designee (Pfizer CRU).

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor's designee (Pfizer CRU).

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

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

10.1.9. Use of Medical Records

There may be instances when copies of medical records for certain cases are requested by Pfizer Safety, where ethically and scientifically justified and permitted by local regulations, to ensure participant safety.

Due to the potential for a participant to be re-identified from their medical records, the following actions must be taken when medical records are sent to the sponsor or sponsor designee:

- The investigator or site staff must redact personal information from the medical record. The personal information includes, but is not limited to, the following: participant names or initials, participant dates (eg, birth date, date of hospital admission/discharge, date of death), participant identification numbers (eg, Social Security number, health insurance number, medical record number, hospital/institution identifier), participant location information (eg, street address, city, country, postal code, IP address), participant contact information (eg, telephone/fax number, email address).

- Each medical record must be transmitted to the sponsor or sponsor designee using systems with technical and organizational security measures to ensure the protection of personal data (eg, Florence is the preferred system if available).

There may be unplanned situations where the sponsor may request medical records (eg, sharing medical records so that the sponsor can provide study-related advice to the investigator). The medical records should be submitted according to the procedure described above.

10.1.10. Study and Site Start and Closure

The study start date is the date of the first participant's first visit.

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, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;

- Inadequate recruitment of participants by the investigator;

- Discontinuation of further study intervention development.

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

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

10.1.11. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer 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 intervention or Pfizer related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

10.1.12. Sponsor's Medically Qualified Individual

The contact information for the sponsor's MQI for the study is documented in the study contact list located in the SToD team Roster.

To facilitate access to their investigator and the sponsor's MQI for study-related medical questions or problems from non-study healthcare professionals, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week.

The ECC is intended to augment, not replace, the established communication pathways between the participant and their investigator and site staff, and between the investigator and sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, 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 issues.

Table 6. Protocol Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN/urea and creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein Direct bilirubin[h] Indirect bilirubin Cystatin C	<u>Local dipstick:</u> pH[a] Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Spot urine <u>Laboratory:</u> Microscopy[b]	• Urine drug screening[c] • Pregnancy test (β-hCG)[d] • eGFR-CKD-EPI 2021 <u>At screening only:</u> • Serum FSH[e] • Hepatitis B surface antigen[f] • Hepatitis B core antibody[f] • Hepatitis C virus (HCV) RNA • Hepatitis C antibody[f] • Human immunodeficiency virus • QuantiFERON® TB Gold or equivalent[g]

a. Can be performed on dipstick or pH-meter device.
b. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
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.
e. At Screening for confirmation of postmenopausal status only.
f. If HBsAg is negative and HBcAb is positive, HBsAb should be evaluated.
g. Complete at screening. Previous testing for QuantiFERON® TB Gold Test will be accepted if completed within 12 weeks prior to screening. Otherwise, the testing should be completed at screening and results available prior to Day 1.
h. Only if total bilirubin is elevated.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF.

Any remaining serum/plasma from samples collected for clinical safety laboratory measurements at baseline and at all times after dose administration may be retained and stored for the duration of the study. Upon completion of the study, these retained safety samples may be used for the assessment of exploratory safety biomarkers or unexpected safety findings. These data will not be included in the CSR. Samples to be used for this

purpose will be shipped to either a Pfizer approved- BBS facility or other designated laboratory and retained for up to 1 year following the completion of the study.

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 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 an increase in either frequency and/or intensity of the condition.
 	
• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

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

10.3.2. Definition of an SAE

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

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

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

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

g. Other situations:

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

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 using the CT SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

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

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs/SAEs associated with EDP or EDB **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 nonparticipant (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 SAE): is reported to Pfizer Safety using the CT SAE Report Form.

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

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

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE or SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety. Refer to Section 10.1.9 for actions that must be taken when medical records are sent to the sponsor or sponsor designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

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

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual ADL.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADL, causing discomfort, but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual ADL, or significantly affects clinical status, or may require intensive therapeutic intervention.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in their assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have 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 their 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 DCT
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT (eg, eSAE or PSSA). • If the electronic system is unavailable, then the site will use the paper SAE report form (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper form (as applicable) as soon as the data become available. • After the study is completed at a given site, the electronic DCT will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic DCT has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via the CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is one of the methods to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are not required to use contraception in this study, because ritlecitinib is not likely to transfer to a partner through semen at pharmacologically relevant blood levels.

10.4.2. Female Participant Reproductive Inclusion Criteria

The criteria below are part of Inclusion Criterion 1 (Age and Sex; Section 5.1) and specify the reproductive requirements for including female participants. Refer to Section 10.4.4 for a complete list of contraceptive methods permitted in the study.

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 agrees to use an acceptable contraceptive method during the intervention period (for a minimum of 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 or oligomenorrhea) 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. **Premenarchal.**
2. **Premenopausal female with 1 of the following:**
   - Documented hysterectomy;
   - Documented bilateral salpingectomy;
   - Documented bilateral oophorectomy.

For individuals with permanent infertility due to a 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.

3. **Postmenopausal female.**

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:

        - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.

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

10.4.4. Contraception Methods

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

The following contraceptive methods are appropriate for this study:

<u>Highly Effective Methods That Have Low User Dependency</u>

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

2. Intrauterine device.

3. Intrauterine hormone releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner:

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has

been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

6. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation used in combination with a barrier method:
   - Oral + barrier*;
   - Intravaginal + barrier*;
   - Transdermal + barrier*.
7. Progestogen only hormone contraception associated with inhibition of ovulation used in combination with a barrier method:
   - Oral + barrier*;
   - Injectable + barrier*.

Sexual Abstinence

8. 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.

* Acceptable barrier methods to be used concomitantly with options 6 or 7 for the study include any of the following

- Male or female condom, with or without spermicide.
- Cervical cap, diaphragm, or sponge with spermicide.

Male condom and female condoms should not be used together (due to risk of failure with friction).

10.5. Appendix 5: Genetics

Use/Analysis of DNA

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

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

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

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

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

- The samples will be retained as indicated:

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

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

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

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

Potential Cases of Drug-Induced Liver Injury

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

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili 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 T bili 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 T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili 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** T bili 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 T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

Rises in AST/ALT and T bili 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 T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, eosinophils (%), and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, total bile acids, 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 T bili 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: Kidney Safety: Monitoring Guidelines

10.7.1. Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury

Standard kidney safety monitoring requires assessment of baseline and postbaseline Screat measurement to estimate kidney function [Screat-based eGFR] or creatinine clearance [eCrCl]). Obtaining Screening or Baseline Scys and postbaseline reflex Scys (if confirmed Screat increase ≥0.3 mg/dL) makes it feasible to distinguish AKI from DICI. If Screat increase is confirmed after baseline, then reflex measurement of Scys is indicated:

ADULTS: Currently, 2021 CKD-EPI eGFR equations (Screat only-based and combined Screat plus Scys-based) are valid for use in adults only. At baseline Screat and Scys values are needed to calculate 2021 CKD-EPI eGFR by Screat only-based equation (see Section 10.7.2.1) and by combined Screat plus Scys-based equation. When post-baseline Screat increase ≥0.3 mg/dL is confirmed, then reflex Scys measurement is needed to enable post-baseline comparison of eGFR changes (Screat only-based eGFR and combined Screat plus Scys eGFR).

Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

10.7.2. Age-Specific Kidney Function Calculation Recommendations

10.7.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations

eGFR (mL/min/1.73m²)[2]

2021 CKD-EPI Screat Only	**Screat** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤ 0.7	NA	$eGFR = 143 \times (Screat/0.7)^{-0.241} \times (0.9938)^{Age}$
Female	if > 0.7	NA	$eGFR = 143 \times (Screat/0.7)^{-1.200} \times (0.9938)^{Age}$
Male	if ≤ 0.9	NA	$eGFR = 142 \times (Screat/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if > 0.9	NA	$eGFR = 142 \times (Screat/0.9)^{-1.200} \times (0.9938)^{Age}$
2021 CKD-EPI Screat-Scys Combined	**Screat** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤ 0.7	if ≤ 0.8	$eGFR = 130 \times (Screat/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if ≤ 0.7	if > 0.8	$eGFR = 130 \times (Screat/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	if > 0.7	if ≤ 0.8	$eGFR = 130 \times (Screat/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if > 0.7	if > 0.8	$eGFR = 130 \times (Screat/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if ≤ 0.8	$eGFR = 135 \times (Screat/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if > 0.8	$eGFR = 135 \times (Screat/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if > 0.9	if ≤ 0.8	$eGFR = 135 \times (Screat/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if > 0.9	if > 0.8	$eGFR = 135 \times (Screat/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

10.7.3. Kidney Function Calculation Tools

The sponsor has provided the following resources to investigational sites when required to calculate age-specific kidney function at Screening, Baseline, and post-Baseline visits. Site calculations of kidney function can be performed manually, using the age appropriate formulae (see Section 10.7.2) and can use recommended online kidney function calculators to reduce the likelihood of a calculation error.

The United States National Kidney Foundation Online Calculators.

- Adults (18 years and above) - 2021 CKD-EPI Creatinine Online Calculator (eGFR): https://www.kidney.org/professionals/KDOQI/gfr_calculator

Investigational sites are responsible to ensure that the accurate age-specific equation is selected and that the correct units are used for serum creatinine (mg/dL only), serum cystatin C (mg/L only), total body weight (kg only), and age (years). Investigators are expected to (i) review and confirm correctness of the kidney function calculation results and (ii) evaluate the calculated value within the context of historical information available to them in the participant's medical record. Investigators are responsible for the clinical oversight of the participant eligibility process, kidney function calculation, and dose selection and adjustments per study protocol. Investigators are encouraged to direct questions or uncertainties regarding kidney function and dosing to the Pfizer Clinical Team and Medical Monitor, if needed.

10.7.4. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl) will be according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria for both pediatric and adult participants.

KDIGO criteria grade (G)	**Study Population**	**G1**	**G2**	**G3**	**G4**	**G5**
Decreased Kidney Function due to either Acute or Chronic Kidney Injury	Adult participants eGFR (mL/min/1.73m²)	≥90	≥60 to 89	30 to 59	15 to 29	<15

KDIGO albuminuria (A) criteria	**A1**	**A2**	**A3**
Albumin-to-creatinine ratio (ACR)	<30 mg/g OR <3 mg/mmol	30 to 300 mg/g OR 3 to 30 mg/mmol	>300 mg/g OR >30 mg/mmol

CTCAE Term (2017)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
AKI	NA	NA	Hospitalization indicated	Life-threatening consequences; dialysis indicated	Death
AKI: A disorder characterized by acute loss of kidney function (within 2 weeks) and is traditionally classified as pre-renal (low blood flow into kidneys), renal (kidney damage), or post-renal causes (ureteral or bladder outflow obstruction.					
Creatinine increased	>ULN to 1.5 × ULN	>1.5 to 3.0 × baseline OR >1.5 to 3.0 × ULN	>3.0 to 6.0 × baseline OR >3.0 to 6.0 × ULN	>6.0 × ULN	NA
CKD	eGFR ≥60 to 89 mL/min/1.73m² OR eCrCl ≥60 to 80 mL/min	eGFR 30 to 59 mL/min/1.73m² OR eCrCl 30 to 59 mL/min	eGFR 15 to 29 mL/min/1.73m² OR eCrCl 15 to 29 mL/min	eGFR <15 mL/min/1.73m² OR eCrCl <15 mL/min OR dialysis indicated	Death
Proteinuria	ADULTS: Proteinuria 1+ OR Proteinuria >0.5 to <1.0 g/24 h	ADULTS: Proteinuria 2+ or 3+ OR Proteinuria 1.0 to <3.5 g/24 h	ADULTS: Proteinuria 4+ OR Proteinuria ≥3.5 g/24 h	NA	NA
CKD: A disorder characterized by gradual and usually permanent loss of kidney function resulting in kidney failure.					

10.8. Appendix 8: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 ms. • New prolongation of QTcF to >480 ms (absolute). • New prolongation of QTcF by >60 ms 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-second duration. • Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as SAEs

• QTcF prolongation >500 ms.
• Absolute value of QTcF > 450 ms AND QTcF change from baseline >60 ms.
• New ST-T changes suggestive of myocardial ischemia.
• New onset- LBBB (QRS complex>120 ms).
• New onset- right bundle branch block (QRS complex>120 ms).
• Symptomatic bradycardia.
• Asystole
  • In awake, symptom-free- participants in sinus rhythm, with documented asystolic pauses ≥3 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 asystolic pauses of at least 5 seconds or longer.
• Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.

- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

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

The major events of potential clinical concern listed above 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 is to be reported as AEs/SAEs.

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/activities of daily living
AE	adverse event
AKI	acute kidney injury
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{inf}	area under the plasma concentration-time profile from time 0 extrapolated to infinite time
AUC_{last}	area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration
AV	atrioventricular
AxMP	auxiliary medicinal product
BAEP	brainstem auditory evoked potential
β-hCG	β-human chorionic gonadotropin
BID	twice a day
BMI	body mass index
BP	blood pressure
Bpm	beats per minute
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
CL/F	Apparent clearance after oral dose
C_{max}	maximum observed concentration
CNS	central nervous system
CO_2	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRU	clinical research unit

Abbreviation	Term
CSR	Clinical Study Report
CT	clinical trial
CTIS	Clinical Trial Information System
DCT	data collection tool
DICI	drug-induced creatinine increase
DIKI	drug-induced kidney injury
DILI	drug-induced liver injury
DR	dose ranging
EBV	Epstein Barr Virus
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
EDR	extemporaneous dispensing record
eGFR	estimated glomerular filtration rate
eSAE	electronic serious adverse event
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IL	interleukin

Abbreviation	Term
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IP	investigational product
IPAL	Investigational Product Accountability Log
IR	immediate release
IRB	Institutional Review Board
JAK	Janus kinase
KDIGO	Kidney Disease Improving Global Outcomes
k_{el}	first-order elimination rate constant
$t_{½}$	terminal phase half-life
LBBB	left bundle branch block
LFT	liver function test
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MMR	measles, mumps, rubella
MQI	medically qualified individual
MR	modified release
NA (N/A)	not applicable; not available
NIMP	non-investigational medicinal product
NOAEL	no-observed-adverse-effect level
PCRU	Pfizer Clinical Research Unit
PD	pharmacodynamic(s)
PI	principle investigator
PK	pharmacokinetic(s)
PNS	peripheral nervous system
PO	orally
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PVC	premature ventricular contraction/complex
QD	Once a day
QFT-G	QuantiFERON®-TB Gold In-Tube
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
qual	qualitative
RA	rheumatoid arthritis
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan

Abbreviation	Term
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
Scys	serum cystatin C
SoA	schedule of activities
SOP	standard operating procedure
SRSD	Single Reference Safety Document
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	tuberculosis
T bili	total bilirubin
TEAE	treatment-emergent adverse events
TEC	tyrosine kinase expressed in hepatocellular carcinoma
THC	tetrahydrocannabinol
T_{lag}	time before the first concentration above the limit of quantification or above the first concentration in the interval
T_{max}	time for maximum plasma concentration
TP	treatment period
TYK	tyrosine kinase
ULN	upper limit of normal
UC	ulcerative colitis
URTI	upper respiratory tract
US	United States
V_z/F	apparent volume of distribution
WBC	white blood cell
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of non childbearing potential

11. REFERENCES

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