A PHASE 1, RANDOMIZED, OPEN-LABEL, CROSS-OVER, SINGLE DOSE STUDY TO ESTIMATE THE RELATIVE BIOAVAILABILITY OF PEDIATRIC RITLECITINIB (PF-06651600) CAPSULES AND SPRAY CONGEALED BEADS RELATIVE TO ADULT CAPSULES IN HEALTHY ADULT PARTICIPANTS

Study Intervention Number:	PF-06651600
Study Intervention Name:	Ritlecitinib
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Phase:	1

Short Title: RELATIVE BIOAVAILABILITY STUDY IN HEALTHY PARTICIPANTS OF PEDIATRIC RITLECITINIB (PF-06651600) CAPSULES AND SPRAY CONGEALED BEADS RELATIVE TO ADULT CAPSULES

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Amendment 1	11 August 2021	• In Section 1.1 Synopsis, Section 1.3 SOA, Section 3 Objectives and Endpoints, Section 4.1 Overall Design, Section 8.11 Taste Assessment, Section 9.4.4 Taste Assessment Analyses, added taste assessment as an "Other" endpoint. Rationale: Spray congealed beads are a new formulation being evaluated. Taste assessment is included to enable evaluation of the taste characteristics. • In Section 5.2, Exclusion Criterion #21, the eGFR cutoff was revised to <60 ml/min. Rationale: eGFR ≥60 ml/min is considered within the normal range per current Pfizer guidance for healthy participant studies. • Added Appendix 9 Taste Assessment Questionnaire Rationale: Taste Assessment Questionnaire is the tool for assessing the taste characteristics of the spray congealed beads. • Revised language in Section 2.2.4.3.3 Phase 2a Study in Alopecia Areata Rationale: To improve readability
Original protocol	12 October 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: RELATIVE BIOAVAILABILITY STUDY IN HEALTHY PARTICIPANTS OF PEDIATRIC RITLECITINIB (PF-06651600) CAPSULES AND SPRAY CONGEALED BEADS RELATIVE TO ADULT CAPSULES

Rationale

Ritlecitinib (PF-06651600) is a covalent and irreversible inhibitor of JAK3 with high selectivity over the other JAK isoforms (JAK1, JAK2, and TYK2). Ritlecitinib (PF-06651600) also inhibits irreversibly the TEC family kinases with selectivity over the broader human kinome. Treatment with ritlecitinib (PF-06651600) 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 (PF-06651600) 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.

A capsule formulation of the tosylate salt of ritlecitinib (PF-06651600) has been developed and nominated to be the marketed dosage form and is being evaluated in a pivotal BE trial relative to the tablets. The tablet formulation is the current clinical product at strengths of 10 mg and 50 mg. A 10 mg capsule and a spray congealed bead are being evaluated as potential candidate formulations for pediatric patients. Both these formulations have qualitative and quantitative differences in their formulation excipients from the adult capsules. The primary objective of this study is to obtain an estimate of the bioavailability of a single oral dose of pediatric ritlecitinib (PF-06651600) capsules (3 × 10 mg capsules) relative to the 30 mg adult capsule in healthy adult participants under fasting conditions. Additionally, an alternative pediatric formulation utilizing a spray congealed beads will also be evaluated.

Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
• To estimate the relative BA of ritlecitinib (PF-06651600) pediatric capsules (3 × 10 mg capsule, Test) relative to adult 30 mg capsule (Reference) under fasted conditions in healthy adult participants. • To estimate the relative BA of ritlecitinib (PF-06651600) administered as 30 mg spray congealed beads (Test) relative to adult 30 mg capsule (Reference) under fasted conditions in healthy adult participants.	• Plasma AUC_{inf} and C_{max} for ritlecitinib (PF-06651600).
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of 10 mg capsules, 30 mg capsules and spray congealed beads at the 30 mg dose of ritlecitinib (PF-06651600) administered to healthy adult participants under fasted conditions.	• Safety laboratory tests and AE monitoring.
Other:	**Other:**
• To characterize the PK of ritlecitinib (PF-06651600) administered as pediatric capsules (3 × 10 mg capsule), adult 30 mg capsule and 30 mg spray congealed beads in healthy adult participants under fasted conditions. • To assess the sensory characteristics and overall palatability of spray congealed beads by healthy participants.	• T_{max}, AUC_{last}, $t_{½}$ (if data permit) and other PK parameters such as CL/F, V_z/F. • Responses to the taste assessment questionnaire that document overall liking, mouth feel, bitterness, sourness, saltiness and tongue/mouth burn of sensory attributes.

Overall Design

The study will be conducted as a Phase 1, open-label, single dose, randomized, 3 period, cross-over design in a single cohort of approximately 12 healthy male or female participants at a single center. Participants will be randomized into 2 sequences of treatment as described in the following table of Intervention Groups and Duration.

Number of Participants

A total of approximately 12 participants will be randomly assigned to study intervention such that approximately 6 participants will be enrolled to 1 of the 2 sequences.

Participants who withdraw from the study may be replaced at the discretion of the investigator upon consultation with the sponsor.

Intervention Groups and Duration

Treatment Sequence	Period 1	Washout	Period 2	Washout	Period 3
1 (n=6)	A	At least 2 days of washout between dosing	B	At least 2 days of washout between dosing	C
2 (n=6)	B		A		C

n = number of participants.
Treatment A: ritlecitinib (PF-06651600) 30 mg intact adult capsule
Treatment B: ritlecitinib (PF-06651600) 3 × 10 mg pediatric capsules
Treatment C: ritlecitinib (PF-06651600) 30 mg spray congealed beads

Since ritlecitinib (PF-06651600) is rapidly eliminated ($t_{½}$ ~2 hours), there will be at least a 2-day washout between each dose.

Blood samples for PK analysis will be collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16 and 24 hours post-dose.

A taste assessment will be conducted using a taste assessment questionnaire for the spray congealed beads in Period 3, immediately after dosing, and at 5 min, 10 min, 20 min after dosing.

Participants will participate in the study up to approximately 2.5 months, including the screening and follow-up periods. Participants will be screened within 28 days of the first dose of study intervention and if all entry criteria are fulfilled, the participants will report to the CRU on the day prior to Period 1 Day 1 dosing (Day -1). On Day 1 of each period, participants will receive a single dose of study intervention. Capsules and spray congealed beads will be administered with approximately 240 mL of ambient temperature water and will be swallowed (not chewed). Participants will be fasted for at least 10 hours pre-dosing and 4 hours post-dosing.

Participants will be confined in the CRU for a total of at least 7 days (6 nights which includes admission to the CRU on Day -1) and discharged at the discretion of the investigator. A follow-up phone call will be made at least 28 calendar days and up to 35 calendar days after the last administration of the study interventions to capture any potential AE and confirm appropriate contraceptive usage.

Data Monitoring Committee or Other Independent Oversight Committee

Not Applicable.

Statistical Methods

The following table presents the width of 90% confidence interval for different estimated effects for a sample size of 12 participants:

Parameter	Estimated Effect (100*Test/Reference)	90%CI	CI Width
AUC	85%	77.0%, 93.9%	16.9%
	90%	81.5%, 99.4%	17.9%
	95%	86.0%, 104.9%	18.9%
	100%	90.6%, 110.4%	19.9%
	105%	95.1%, 115.9%	20.9%
	110%	99.6%, 121.5%	21.9%
	115%	104.1%, 127.0%	22.8%
C_{max}	85%	69.7%, 103.6%	33.9%
	90%	73.8%, 109.7%	36.9%
	95%	77.9%, 115.8%	37.9%
	100%	82.0%, 121.9%	39.9%
	105%	86.1.6%, 128.0%	41.9%
	110%	90.2%, 134.1%	43.9%
	115%	94.3%, 140.2%	45.9%

These calculations are based on the estimates of within-subject standard deviations of 0.106 and 0.212 for ritlecitinib (PF-06651600) $\log_e AUC_{inf}$ and $\log_e C_{max}$, respectively, as obtained from studies B7981003 and B7981022.

Participants may be replaced at the discretion of the sponsor.

To estimate the relative BA of ritlecitinib (PF-06651600) pediatric capsule (3 × 10 mg capsules) relative to adult 30 mg capsule, the natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effects model with sequence, period and treatment as fixed effects and participant within sequence as a random effect. 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. Treatment A (30 mg capsule form of ritlecitinib [PF-06651600] under fasted conditions) will be the Reference treatment while Treatment B (3 × 10 mg pediatric capsules of ritlecitinib [PF-06651600] under fasted conditions) will be the Test treatment. Data from Period 3 (Treatment C) will be excluded from this analysis.

To estimate the relative BA of ritlecitinib (PF-06651600) administered as 30 mg spray congealed beads (Test) relative to adult 30 mg capsule (Reference) under fasted conditions, the natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effects model with sequence and treatment as fixed effects and participant within sequence as a random effect. 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. Treatment A (30 mg capsule of ritlecitinib [PF-06651600] under fasted conditions) will be the Reference treatment while Treatment C (30 mg spray congealed beads of ritlecitinib [PF-06651600] under fasted conditions) will be the Test treatment.

Taste Assessment Analyses

The data used in the analysis will be transcribed and rescaled to a score from 0 to 100 from the raw measurements on the taste questionnaire. The sensory attributes (overall liking, mouth feel, bitterness, sourness, saltiness, tongue/mouth burn) from the taste questionnaire (Appendix 9) for Treatment C (30 mg spray congealed beads) will be listed and descriptively summarized by collection time. Radar plots for each time point, summarizing all attributes, will be generated.

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 10	**Screening**[a]	**Treatment Period**								
		Period 1			**Period 2**		**Period 3**		**Follow-up**[b]	**Early Termination/ Discontinuation**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 1**	**Day 2**	**Day 1**	**Day 2**	**Telephone Contact**	
Study Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**33 to 40**	
Informed consent	X									
CRU confinement		X	→	→	→	→	→	X		
Inclusion/exclusion criteria	X	X[c]								
Demographic information[d]	X									
Medical/medication, drug, tobacco and alcohol history (update)[e]	X	X[c]								
Complete/limited physical examination[f]	X	X						X		X
Safety laboratory[g]	X	X						X		X
Pregnancy test (WOCBP only)	X	X						X		X
Contraception check[h]	X	X						X	X	X
FSH (post-menopausal women only)	X									
Urine drug testing	X	X								
12-Lead ECG[i]	X		X[o]					X		X
Blood pressure and pulse rate, temperature[j]	X		X[o]					X		X
HIV, HCVAb, HBsAg, HbcAb[k]	X									

Visit Identifier Abbreviations used in this table may be found in Appendix 10	Screening[a]	Treatment Period								
		Period 1			Period 2		Period 3		Follow-up[b]	Early Termination/ Discontinuation
Days Relative to Day 1	Day -28 to Day -2	Day -1	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2	Telephone Contact	
Study Day	-28 to -2	-1	1	2	3	4	5	6	33 to 40	
TB screening (QuantiFERON® Gold Test)	X									
Lipid panel[g]	X									
Study intervention administration[l]			X		X[p]		X[p]			
Taste assessment							X[q]			
Pharmacokinetic blood sampling[m]			X	X	X	X	X	X		
Pfizer Prep D1 Banked Genetic Biospecimens[n]			X[o]							
Prior/concomitant treatments	X	X	X					X	X	X
CRU discharge								X		
Serious and nonserious adverse event monitoring	X	X	→	→	→	→	→	X	X	X

a. Participants will be screened within 28 days of the first dose of study intervention.
b. Follow-up contact will occur by telephone and must occur at least 28 to 35 days after the last administration of ritlecitinib (PF-06651600).
c. Update since screening, if applicable.
d. Including measurement of height and weight at screening.
e. 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 would be reviewed or updated only.
f. Complete (full) physical examination must either be conducted at Screening or upon Admission of Period 1 (Day -1) only; limited physical examination is required upon discharge/early termination/discontinuation; brief (limited) physical examination may be performed as appropriate at other times at the investigator's discretion if there are findings during the previous examination, new/open adverse events.
g. Safety laboratory testing must be collected within 28 days prior to first administration of study medication (see Section 8.2.4). Safety laboratory assessments including urinalysis, hematology, and chemistry will be performed following at least 4 hours fasting; however, the lipid profile requires fasted conditions for at least 10 hours. Samples will be collected prior to discharge or if the reason for discontinuation is related to an AE. Additional laboratory assessments may be required to evaluate potential case of Hy's Law or adverse event as deemed necessary by the investigator. Refer to Table 4 in Section 10.2.
h. The contraception check is an opportunity to confirm that contraception, if assigned, is used consistently and correctly.
i. Single ECG will be used.
j. Single BP will be collected in the supine position.
k. For hepatitis B, all participants will undergo testing at screening for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb); If HBsAg is negative and HBcAb is positive, HBsAb should be evaluated.
l. Participants assigned to receive study intervention under fasted conditions must be fasted for at least 10 hours pre-dosing and 4 hours post-dosing.

Visit Identifier Abbreviations used in this table may be found in Appendix 10	Screening[a]	Treatment Period								
		Period 1			Period 2		Period 3		Follow-up[b]	Early Termination/ Discontinuation
Days Relative to Day 1	Day -28 to Day -2	Day -1	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2	Telephone Contact	
Study Day	-28 to -2	-1	1	2	3	4	5	6	33 to 40	

m. PK dosing will be captured on the day of dosing at the following timepoints: pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16 and 24 hours post-dose.
n. If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.
o. Collected at pre-dose.
p. Dosing of each period to be separated by at least a 48-hour washout interval. The participants will be discharged on Day 2 of Period 3.
q. Review taste assessment questionnaire and instructions with participants prior to dosing in Period 3, Day 1. Each participant will record the sensory attributes at timed intervals of 0 (immediately after dosing), 5, 10 and 20 minutes after administration using a taste assessment questionnaire (see Appendix 9).

Table 1. Pharmacokinetic Sampling Schema for Period 1, Period 2 and Period 3

Visit Identifier	Period 1, Period 2 and Period 3												
Study Day	1												2
Hours Before/After Dose	0[a]	0.25	0.5	1	1.5	2	3	4	6	9	12	16	24
Study Intervention Administration	X												
Ritlecitinib (PF-06651600) PK blood sampling[b]	X	X	X	X	X	X	X	X	X	X	X	X	X

a. Predose PK samples. Any time prior to dosing ritlecitinib (PF-06651600) on the day of dosing.
b. Ritlecitinib (PF-06651600) PK blood samples (2 mL blood to yield approximately 0.5 mL plasma) are to be collected.

2. INTRODUCTION

Ritlecitinib (PF-06651600) 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 proposed pediatric formulation for ritlecitinib (PF-06651600) is a 10 mg capsule administered intact or sprinkled over food. The primary objective of this study is to obtain an estimate of the bioavailability of pediatric ritlecitinib (PF-06651600) capsules relative to the adult capsule in healthy participants. Also, an alternative formulation utilizing spray congealed beads will be evaluated.

2.2. Background

Ritlecitinib (PF-06651600) is a covalent and irreversible inhibitor of JAK3 with high selectivity over the other JAK isoforms (JAK1, JAK2, and TYK2). Ritlecitinib (PF-06651600) also inhibits irreversibly the tyrosine kinase expressed in TEC family kinases with selectivity over the broader human kinome. Treatment with ritlecitinib (PF-06651600) 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 (PF-06651600) 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 (PF-06651600) can be found in the current IB.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

Details of the nonclinical PK and metabolism of ritlecitinib (PF-06651600) 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 44-fold exposure multiple in the rat study and a 6.5-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 central nervous system and the peripheral nervous system at ≥20 mg/kg/day, accompanied by functional auditory deficits (brainstem auditory evoked potentials) at the highest dose of 40 mg/kg/day (a 29-fold exposure multiple relative to the clinical dose of 50 mg).

Further information is available in the current version of the ritlecitinib (PF-06651600) IB.

2.2.4. Clinical Overview

2.2.4.1. Clinical Overview of Ritlecitinib

Ritlecitinib (PF-06651600) has been evaluated in healthy participants in a FIH B7981001 study, in a BA B7981003 study which compared the relative BA of solution versus tablet, and a PK study in Japanese participants (B7981008). It has also been evaluated in participants with moderate to severe RA in B7981006, and moderate to severe AA in B7931005. Study B7981022 compared the relative BA of capsule versus tablet. Besides, there are ongoing studies in participants with moderate to severe AA (B7981015), moderate to severe active UC (B7981005), active non-segmental vitiligo (B7981019), and moderate to severe active CD (B7981007).

2.2.4.2. Pharmacokinetic Overview of Ritlecitinib

The PK profile of ritlecitinib (PF-06651600) is characterized by rapid absorption, rapid elimination (terminal half-life [$t_{½}$] of ~2 hours) and are approximately dose proportional. Steady state generally appears to have been reached by Day 4 for the QD regimens and Day 6 for the BID regimens based on similar median trough (pre-dose) ritlecitinib (PF-06651600) beyond Day 6. Ritlecitinib (PF-06651600) 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 (PF-06651600) in humans appear to be primarily by metabolism. Less than 10% of ritlecitinib (PF-06651600) is excreted unchanged in the urine.

2.2.4.3. Safety Overview of Ritlecitinib

2.2.4.3.1. Studies in Healthy Participants

The FIH study (B7981001) was a Phase 1, randomized, double-blind, third party open, placebo controlled, single and multiple dose escalation, parallel group study in healthy adult participants. During the single dose period, participants received doses of 5, 20, 50, 100, 200, 400, or 800 mg of ritlecitinib (PF-06651600) in a dose escalation format. Participants returned for the multiple dose period to receive doses of 50, 200, or 400 mg QD or 100 or 200 mg BID for 14 days.

B7981008 study was a Phase 1, randomized, double-blind, third–party open, placebo-controlled study to evaluate the safety, tolerability, PK and PD after multiple oral doses of ritlecitinib (PF-06651600) in healthy Japanese adult participants. Six participants were randomized, with 2 participants receiving placebo and 4 participants receiving ritlecitinib (PF-06651600) 200 mg QD, respectively.

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

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 (PF-06651600). Each study included 12 to 14 healthy participants.

In all the above studies, ritlecitinib (PF-06651600) was found to be well tolerated and to have an acceptable safety profile.

2.2.4.3.2. Phase 2a Study in Rheumatoid Arthritis

The completed Phase 2a study B7981006 was an 8-week randomized, double-blind, placebo-controlled, parallel-group, multi-center study in participants with moderate-to-severe active RA with an inadequate response to methotrexate. A total of 70 participants were randomized to study treatment; 28 participants received placebo and 42 participants received ritlecitinib (PF-06651600). Participants remained on stable background arthritis therapy, which had to include methotrexate (supplemented with folic/folinic acid per the local treatment guidelines).

Ritlecitinib (PF-06651600) 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 (PF-06651600) compared to those receiving placebo. The TEAEs reported in more than 5% (1 in 20) participants with RA receiving ritlecitinib (PF-06651600) were influenza and lymphopenia. The majority of the AEs were mild in severity. There was 1 mild case of herpes simplex in the ritlecitinib (PF-06651600) group that was considered to be treatment -related with no cases in the placebo group. There were no clinically relevant changes in vital signs, ECG, or audiometric assessments. By the Week 8 time point (as early as 2 weeks), in the ritlecitinib (PF-06651600) group, there were decreases in the median platelet counts (25% change from baseline), lymphocyte counts (21% change from baseline), neutrophil counts (24% change from baseline), and hemoglobin (3% change from baseline). None of these were deemed to be clinically relevant by the investigator and values returned to near baseline by the 12-week follow-up visit.

2.2.4.3.3. Phase 2a Study in Alopecia Areata

Study B7931005 is a completed Phase 2a, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety profile of ritlecitinib (PF-06651600) and PF-06700841 (a TYK2/JAK1 inhibitor) in participants with moderate to severe AA. The study consists of the initial 24-week double-blind treatment period, an up to 12-month single-blind extension period, and a 6-month crossover open-label extension period. A total of 142 participants were randomized to study treatment; 47 participants received placebo, 48 participants received ritlecitinib (PF-06651600), and 47 participants received PF-06700841.

During the initial 24-week double-blind treatment period, participants in the ritlecitinib (PF-06651600) group were treated with 200 mg of ritlecitinib (PF-06651600) QD during a 4-week induction phase, followed by dosing with 50 mg QD in a maintenance phase. At

Week 24, an interim analysis provided data on both efficacy and safety, and indicated clinical improvement for participants treated with ritlecitinib (PF-06651600).

During the initial 24-week treatment period of Study B7931005, there were no deaths and no participant in the ritlecitinib (PF-06651600) treatment group experienced a SAE. The proportion of participants who experienced TEAEs in the placebo treatment group (74.5%) was comparable with the ritlecitinib (PF-06651600) treatment group (62.5%). The TEAEs reported in more than 5% (1 in 20) participants with AA receiving ritlecitinib (PF-06651600) were headache, infections of upper respiratory tract, acne, diarrhea, nausea, and skin infections. The majority of events were mild. No serious infections, malignancies, cases of herpes zoster, or cases of herpes simplex were reported in the ritlecitinib (PF-06651600) group. Hematological changes were observed in both active groups during the induction and maintenance periods, but were not associated with clinically relevant TEAEs. During the induction period, when participants received ritlecitinib (PF-06651600) 200 mg QD for 4 weeks, decreases in mean platelet and lymphocyte counts (-18% and -24% mean change from baseline, respectively) were observed in the ritlecitinib (PF-06651600) group. During the maintenance period, when participants received 50 mg QD for 20 weeks, there was improvement in the platelet and lymphocyte counts in the ritlecitinib (PF-06651600) group. Neutrophil counts were increased at Week 4 (12% change from baseline) and Week 24 (10% change from baseline) in the ritlecitinib (PF-06651600) treatment group. Two participants in the ritlecitinib (PF-06651600) group discontinued due to TEAEs.

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

More detailed information about ritlecitinib (PF-06651600) can be found in in the current version of the ritlecitinib (PF-06651600) IB, which is the SRSD for this study.

2.3. Benefit/Risk Assessment

Ritlecitinib (PF-06651600) is not expected to provide any clinical benefit to healthy participants of this study. This study is designed primarily to generate PK data for further JAK3 development. In this study, ritlecitinib (PF-06651600) will be administered at single doses of 30 mg.

Ritlecitinib (PF-06651600) was determined to be well tolerated and to have an acceptable safety profile in the clinical studies. Reductions in platelet counts and lymphocyte counts were observed during treatment with 200 mg QD, but were not considered clinically meaningful and improved after switching to 50 mg QD. Ritlecitinib (PF-06651600) 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 and evaluated in longer term studies of ritlecitinib (PF-06651600).

In animals, ritlecitinib (PF-06651600) was associated with fetal changes in bones and some internal organs, and lower fetal body weights. It is not known whether ritlecitinib (PF-06651600) is secreted into human milk. Because of that and because of the investigational nature of ritlecitinib (PF-06651600), 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 (PF-06651600) is not likely to transfer to a partner through semen at pharmacologically relevant blood levels.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of ritlecitinib (PF-06651600) may be found in the IB, which is SRSD for this study.

Overall, single doses of ritlecitinib (PF-06651600) of 30 mg in healthy participants are expected to be safe and well tolerated in this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention ritlecitinib (PF-06651600)		
Reductions in platelet counts and lymphocyte counts.	In B7931005 study, reductions in platelet counts and lymphocyte counts were observed during treatment with 200 mg QD, but were not considered clinically meaningful and improved after switching to 50 mg QD.	Clinical laboratory results will be monitored.
Potential risk of infections.	Ritlecitinib (PF-06651600) is an immunomodulator and, as such, can be associated with the potential risk of infections (including serious infections), opportunistic infections, and viral reactivation.	Participants with infection history will be excluded (See Section 5.2) and the risk of infection will be monitored in the study.
Potential fetal risk.	In animals, ritlecitinib (PF-06651600) was associated with fetal changes in bones and some internal organs, and lower fetal body weights. When male rats were treated with ritlecitinib (PF-06651600) and mated with female rats that	WOCBP who are unwilling or unable to use contraception as defined in the study protocol will be excluded (See Section 5.3.4. and Appendix 4).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention ritlecitinib (PF-06651600)		
	were not treated, there were smaller litter sizes due to fewer fertilized eggs attaching to the wall of the uterus in those female rats. There were no effects on sperm or other features of male reproduction.	
Potential risk of secreting into human milk.	It is not known whether ritlecitinib (PF-06651600) is secreted into human milk.	Ritlecitinib (PF-06651600) should not be administered to breastfeeding women and exposure during breastfeeding should be reported to Pfizer Safety (See Section 8.3.5.2).

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To estimate the relative BA of ritlecitinib (PF-06651600) pediatric capsules (3 × 10 mg capsule, Test) relative to adult 30 mg capsule (Reference) under fasted conditions in healthy adult participants. • To estimate the relative BA of ritlecitinib (PF-06651600) administered as 30 mg spray congealed beads (Test) relative to adult 30 mg capsule (Reference) under fasted conditions in healthy adult participants.	• Plasma AUC_{inf} and C_{max} for ritlecitinib (PF-06651600).
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of 10 mg capsules, 30 mg capsules and spray congealed beads at the 30 mg dose of ritlecitinib (PF-06651600) administered to healthy adult participants under fasted conditions.	• Safety laboratory tests and AE monitoring.
Other:	**Other:**
• To characterize the PK of ritlecitinib (PF-06651600) administered as pediatric capsules (3 × 10 mg capsule), adult 30 mg capsule and 30 mg spray congealed beads in healthy adult participants under fasted conditions. • To assess the sensory characteristics and overall palatability of spray congealed beads by healthy participants.	• T_{max}, AUC_{last}, $t_{½}$ (if data permit) and other PK parameters such as CL/F, V_z/F. • Responses to the taste assessment questionnaire that document overall liking, mouth feel, bitterness, sourness, saltiness and tongue/mouth burn of sensory attributes.

4. STUDY DESIGN

4.1. Overall Design

The study will be conducted as a Phase 1, open-label, single dose, randomized, 3 period, cross-over design in a single cohort of approximately 12 healthy male or female participants at a single center. Participants will be randomized into 2 sequences of treatment as described in Table 2:

Sequence 1 (n=6): A B C

Sequence 2 (n=6): B A C

Table 2. Study Design and Treatments

Treatment Sequence	Period 1	Washout	Period 2	Washout	Period 3
1 (n=6)	A	At least 2 days of washout between dosing	B	At least 2 days of washout between dosing	C
2 (n=6)	B		A		C

n = number of participants.
Treatment A: ritlecitinib (PF-06651600) 30 mg intact adult capsule
Treatment B: ritlecitinib (PF-06651600) 3 × 10 mg pediatric capsules
Treatment C: ritlecitinib (PF-06651600) 30 mg spray congealed beads

Since ritlecitinib (PF-06651600) is rapidly eliminated ($t_{½}$ ~2 hours), there will be at least a 48-hour washout between each dose.

Blood samples for PK analysis will be collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16 and 24 hours post-dose.

Participants will participate in the study up to approximately 2.5 months, including the screening and follow-up periods. Participants will be screened within 28 days of the first dose of study intervention and if all entry criteria are fulfilled, the participants will report to the CRU on the day prior to Period 1 Day 1 dosing (Day -1). On Day 1 of each period, participants will receive a single dose of study intervention. Capsules and spray congealed beads will be administered with approximately 240 mL of ambient temperature water, and will be swallowed (not chewed). Participants will be fasted for at least 10 hours pre-dosing and 4 hours post-dosing.

For the taste assessment in Period 3, participants will be asked to not verbalize their responses and not discuss taste with other participants until after they have filled out the responses in the questionnaire.

Participants will be confined in the CRU for a total of at least 7 days (6 nights which includes admission to the CRU on Day -1) and discharged at the discretion of the investigator. A follow-up phone call will be made at least 28 calendar days and up to 35 calendar days after the last administration of the study interventions to capture any potential AE and confirm appropriate contraceptive usage.

Participants who withdraw from the study may be replaced at the discretion of the sponsor.

4.2. Scientific Rationale for Study Design

A capsule formulation of the tosylate salt of ritlecitinib (PF-06651600) has been developed and nominated to be the marketed dosage form and is being evaluated in a pivotal BE trial relative to the tablets. The tablet formulation is the current clinical product at strengths of 10 mg and 50 mg. A 10 mg capsule and a spray congealed bead are being evaluated as potential candidate formulations for pediatric patients. Both these formulations have

qualitative and quantitative differences in their formulation excipients from the adult capsules.

The intent of the study is to estimate the relative bioavailability of ritlecitinib (PF-06651600) 10 mg capsule that is being developed as the market image/commercial pediatric drug product. An alternate dosage form, spray congealed beads, will also be evaluated for bioavailability relative to the adult 30 mg capsules. The spray congealed beads is being considered as an alternative pediatric formulation.

In an embryo-fetal development study in rats, skeletal malformations and variations and lower fetal body weights were observed at relevant clinical exposures for ritlecitinib (PF-06651600). In rabbits, lower mean fetal body weights and higher incidences of visceral and skeletal malformations and skeletal variations were observed at relevant clinical exposures for PF-06651600. See the IB for further details. Therefore, the use of a highly effective method of contraception is required in WOCBP (see Appendix 4).

The potential risk of exposure to ritlecitinib (PF-06651600) in a sexual partner of a male participant in this study via ejaculate is low, and therefore no contraception use in male participants is required. The calculated safety margin is ≥100-fold between the estimated partner exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies. The safety margin of 100-fold is based on applying a 10-fold safety factor for interspecies extrapolation and a 10-fold safety factor for susceptible populations.[1]

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

4.3. Justification for Dose

The current study will use ritlecitinib (PF-06651600) at a dose of 30 mg which is the lowest strength available for the reference adult capsules. The 30 mg dose of ritlecitinib (PF-06651600) is a clinically relevant dose.

Based on clinical data (single oral doses of ritlecitinib [PF-06651600] 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). The AUC for a ritlecitinib (PF-06651600) 200 mg dose maintains the margins of 14-fold and 2.5-fold to NOAELs in 2-month and 9-month dog toxicology studies, respectively. 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 (PF-06651600) is predicted to be well tolerated at a dose of 30 mg in this relative bioavailability study. Further information is available in the current version of the ritlecitinib (PF-06651600) IB.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last scheduled procedure shown in the SoA and the investigator has reviewed the final safety data and determined that no additional evaluation is required.

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.

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Male and female participants must be 18 to 55 years of age, inclusive, at the time of signing the ICD.

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

Type of Participant and Disease Characteristics:

2. Male and female participants who are healthy as determined by medical evaluation including a detailed medical history, complete (full) physical examination, which includes BP and pulse rate measurement, clinical laboratory tests, and 12-lead ECG.

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

Weight:

4. BMI of 17.5 to 30.5 kg/m^2; and a total body weight >50 kg (110 lb).

Informed Consent:

5. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

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

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

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

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

   a. For hepatitis B, all participants will undergo testing for HBsAg and HBcAb.

      - 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. Only participants who are HCVAb negative are eligible.

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

   - Any infection requiring treatment within 2 weeks prior to admission for Period 1.

- 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.

6. History of febrile illness within 5 days prior to the first dose of study intervention.

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

8. Known 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.

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

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

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

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

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

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

Prior/Concomitant Therapy:

11. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention (refer to Section 6.5 for additional details).

12. Use of medications that prolong the QT interval (a list of these medications can be found at http://www.crediblemeds.org/index.php/login/dlcheck) within 10 days or 5 half-lives (whichever is longer) prior to the first dose of the study intervention, or during the study.

13. Vaccination with live virus, attenuated live virus, or any live viral components 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 with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

15. Known participation in a clinical trial of ritlecitinib (PF-06651600) and participant experienced treatment-related adverse events that led to discontinuation or an SAE.

Diagnostic Assessments:

16. A positive urine drug test.

17. A positive serum pregnancy test.

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

19. Baseline 12-lead ECG that demonstrates:

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

- 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;

- Confirmed QTcF prolongation (>450 milliseconds). If QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTc 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 participants.

20. Long QT Syndrome, a family history of Long QT Syndrome, or a history of Torsades de Pointes.

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

    - AST or ALT level >1.5 × ULN;

    - Total bilirubin level >1.5 × ULN; participants with Gilbert's syndrome would be eligible for this study provided that direct bilirubin is ≤ ULN;

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

    - Platelet count $<150 \times 10^9$/L (150,000 cells/mm^3);

    - WBC count of $<3.0 \times 10^9$/L (3000 cells/mm^3);

    - ANC $<1.5 \times 10^9$/L (<1500 cells/mm^3);

    - ALC $<0.8 \times 10^9$/L (<800 cells/mm^3);

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

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

Other Exclusions:

22. 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).

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

24. Have a history of major organ transplant or hematopoietic stem cell/marrow transplant. Skin grafts are not exclusionary.

25. History of severe allergic or anaphylactic reactions.

26. WOCBP who are unwilling or unable to use a highly effective 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.

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

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

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

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

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 10 hours prior to screening laboratory evaluations and at least 4 hours prior to any subsequent safety laboratory evaluations and 10 hours prior to the collection of the predose PK sample on Day 1 of each Period.

- Water is permitted until 1 hour prior to study intervention administration. Water may be consumed without restriction beginning 1 hour after dosing. Non-caffeinated drinks (except grapefruit or grapefruit - related citrus fruit juices - see below) may be consumed with meals and the evening snack. Fasting prior to clinical laboratory sample collection may be extended beyond 4 hours, as needed.

- Lunch will be provided approximately 4 hours after dosing.

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

- An evening snack may be permitted.

- Participants will be allowed breakfast on Day 2 of each period.

- Participants will refrain from consuming red wine, grapefruit, or grapefruit related citrus fruits (eg, Seville oranges, pomelos, fruit juices) from 7 days prior to the first dose of study intervention and during confinement in the CRU.

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

5.3.2. Caffeine, Alcohol, and Tobacco

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

- Participants will abstain from alcohol for 24 hours prior (or as specified above for red wine) to admission to the CRU and continue abstaining from alcohol and during confinement in the CRU. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

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

5.3.3. Activity

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.

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

5.3.4. Contraception

No contraception methods are required for male participants in the study.

The following applies to female participants who are considered WOCBP.

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant from the permitted list of contraception methods (see Appendix 4 Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the

selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.3.5. Vaccination

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

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

5.4. Screen Failures

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

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

6. STUDY INTERVENTION

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

For the purposes of this protocol, study intervention refers to ritlecitinib (PF-06651600) 10 mg pediatric capsule, ritlecitinib (PF-06651600) 30 mg adult capsule, and ritlecitinib (PF-06651600) 30 mg spray congealed beads.

6.1. Study Intervention(s) Administered

For this study, the study intervention is ritlecitinib (PF-06651600), which will be administered as capsules and sprayed congealed beads. The study intervention will be supplied to the CRU in bulk along with individual dosing containers for unit dosing.

Ritlecitinib (PF-06651600) will be presented to the participants in individual dosing containers.

6.1.1. Administration

Study intervention will be administered orally and according to the conditions described in SoA 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). Investigator site personnel will administer study intervention during each period 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. Administer study intervention according to the IP Manual.

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

6.2. Preparation/Handling/Storage/Accountability

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

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

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

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

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

6. See the IP manual for storage conditions of the study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

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

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

6.2.1. Preparation and Dispensing

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

Ritlecitinib (PF-06651600) capsules and spray congealed beads will be prepared at the CRU in the individual dosing containers, by 2 operators, one of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). Prepared doses will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

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

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

6.4. Study Intervention Compliance

When 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. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5. Concomitant Therapy

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

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

Use of medications that prolong the QT interval (a list of these medications can be found at http://www.crediblemeds.org/index.php/login/dlcheck) are prohibited within 10 days or 5 half-lives (whichever is longer) prior to the first dose of the study intervention, or during the study.

Vaccination with live virus, attenuated live virus, or any live viral components are prohibited within the 6 weeks prior to the first dose of study intervention. (Refer to Section 5.3.5 for additional details).

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. Concomitant drug and non-drug treatment will be collected. All participants will be questioned about concomitant treatment at each clinic visit.

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

6.5.1. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with ritlecitinib (PF-06651600); standard medical supportive care must be provided to manage the AEs.

6.6. Dose Modification

Dose modification for ritlecitinib (PF-06651600) is not allowed.

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following: treatment-related SAEs, serious infections, and other events as described in Section 10.8.2.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is definitively discontinued, the participant will 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.

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- Adverse Event

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

The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal. The participant will be permanently discontinued both from the study intervention and from the study at that time.

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

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the CT SAE Report.

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

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

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

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

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

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

A participant who qualified for this protocol but did not enroll from an earlier cohort/group may be used in a subsequent cohort/group without rescreening, provided laboratory results obtained prior to the first dose administration meet eligibility criteria for this study. In addition, other clinical assessments or specimen collections, eg, banked biospecimens, may be used without repeat collection, as appropriate.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol specified criteria and were performed within the time frame defined in the SoA.

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

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

The total blood sampling volume for individual participants in this study is approximately 110 mL (PK sample volume calculated as approximately 78 mL). The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

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

8.1. Efficacy Assessments

Not Applicable.

8.2. Safety Assessments

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

For safety assessments, baseline is defined as the last predose measurement taken before dosing in Period 1: safety laboratory (Day -1), blood pressure, pulse rate, temperature and 12-Lead ECG (Day 1, predose).

8.2.1. Physical Examinations

A complete (full) physical examination will be completed only at the Screening visit or upon admission to the clinic (Day -1) and 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 (limited) physical examination is required upon discharge/early termination/discontinuation and will include, at a minimum, assessments of general appearance, the respiratory and cardiovascular systems, and participant-reported symptoms. Brief (limited) physical examination may also be performed as appropriate at other times at the investigator's discretion if there are findings during the previous examination, new/open AEs.

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.

8.2.2. Vital Signs

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

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

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

8.2.2.1. Temperature

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

8.2.3. Electrocardiograms

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

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline (Period 1, Day 1 predose) measurements. 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 QTc interval remains ≥60 msec from the baseline and is >450 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTc intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than the criterion listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

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

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

8.2.4. Clinical Safety Laboratory Assessments

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

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

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

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

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

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

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

8.2.5. Estimated Glomerular Filtration Rate

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

CKD-EPI

- If female and SCr is ≤0.7 mg/dL:

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

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

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

- If male and SCr is ≤0.9 mg/dL:

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

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

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

8.2.6. Pregnancy Testing

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

8.3. Adverse Events and Serious Adverse Events

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

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

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

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

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

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator 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 definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

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

8.3.1.1. Reporting SAEs to Pfizer Safety

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

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

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

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.

- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below is an example of environmental exposure during pregnancy:

    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion or skin contact.

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

- If EDP occurs in a participant, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose.

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

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

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

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

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

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

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

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

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

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

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

8.3.6. Cardiovascular and Death Events

Not Applicable

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

Not Applicable

8.3.8. Adverse Events of Special Interest

Not Applicable

8.3.8.1. Lack of Efficacy

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

8.3.9. Medical Device Deficiencies

Not Applicable

8.3.10. Medication Errors

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

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

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

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

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

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

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

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

8.4. Treatment of Overdose

For this study, any dose of ritlecitinib (PF-06651600) greater than 800 mg within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of ritlecitinib (PF-06651600) (whichever is longer).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**
5. Obtain a blood sample for PK analysis within 4 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case by case basis).

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

8.5. Pharmacokinetics

Blood samples of approximately 2 mL, to provide approximately 0.5 mL plasma, will be collected for measurement of plasma concentrations of ritlecitinib (PF-06651600) as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

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

Samples will be used to evaluate the PK of ritlecitinib (PF-06651600). Samples collected for analyses of ritlecitinib (PF-06651600) concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

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

Samples collected for measurement of plasma concentrations of ritlecitinib (PF-06651600) 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 will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

8.7.1. Specified Genetics

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

8.7.2. Banked Biospecimens for Genetics

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

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

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

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are not applicable in this study.

8.10. Health Economics

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

8.11. Taste Assessment

Taste assessment of the spray congealed beads will be conducted in Period 3 with the aid of a questionnaire (Appendix 9). The taste assessment questionnaire will be administered to participants by trained staff using a colored copy of the questionnaire. Participants after drug administration will be asked to rate the overall liking, mouth feel, bitterness, sourness, saltiness and tongue/mouth burn. The participants will rate the above immediately after dosing and at 5 min, 10 min, 20 min after dosing.

See Appendix 9 for the details about the taste assessment questionnaire.

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 statistical hypothesis will be tested in this study.

9.2. Sample Size Determination

The following table presents the width of 90% confidence interval for different estimated effects for a sample size of 12 participants:

Parameter	Estimated Effect (100*Test/Reference)	90%CI	CI Width
AUC	85%	77.0%, 93.9%	16.9%
	90%	81.5%, 99.4%	17.9%
	95%	86.0%, 104.9%	18.9%
	100%	90.6%, 110.4%	19.9%
	105%	95.1%, 115.9%	20.9%
	110%	99.6%, 121.5%	21.9%
	115%	104.1%, 127.0%	22.8%
C_{max}	85%	69.7%, 103.6%	33.9%
	90%	73.8%, 109.7%	36.9%
	95%	77.9%, 115.8%	37.9%
	100%	82.0%, 121.9%	39.9%
	105%	86.1.6%, 128.0%	41.9%
	110%	90.2%, 134.1%	43.9%
	115%	94.3%, 140.2%	45.9%

These calculations are based on the estimates of within-subject standard deviations of 0.106 and 0.212 for ritlecitinib (PF-06651600) $\log_e AUC_{inf}$ and $\log_e C_{max}$, respectively, as obtained from studies B7981003 and B7981022.

Participants who discontinue or withdraw from the study or who are not considered evaluable may be replaced at the discretion of the sponsor.

9.3. Analysis Sets

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

Population	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.
Safety	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.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

An efficacy analysis is not applicable to this study.

9.4.2. Safety Analyses

AEs and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical 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 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.

For safety assessments, baseline is defined as the last predose measurement taken before dosing in Period 1: safety laboratory (Day -1), blood pressure, pulse rate, temperature and 12-Lead ECG (Day 1, predose).

9.4.3. Pharmacokinetic Analyses

PK parameters following a single dose administration will be derived from the concentration time profiles using non-compartmental methods as data permit. The various PK parameters to be assessed in this study, their definition, and method of determination are outlined in Table 3. In all cases, actual PK sampling times will be used in the derivation of PK parameters.

Table 3. Definitions of PK Parameters

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration time profile from time 0 to the time of the last quantifiable concentration (C_{last})	Linear-log trapezoidal method
AUC_{inf}	Area under the plasma concentration-time profile from time 0 extrapolated to infinite time	$AUC_{last} + (C_{last}/k_{el})$ where C_{last} is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis

Table 3. Definitions of PK Parameters

Parameter	Definition	Method of Determination
C_{max}	Maximum plasma concentration	Observed directly from the data
T_{max}	Time for C_{max}	Observed directly from the data as time of first occurrence
$t_{½}$	Terminal elimination half-life	$Log_e(2)/k_{el}$ Only those data points judged to describe the terminal log-linear decline will be used in the regression.
CL/F	Apparent clearance after oral dose	Dose/AUC_{inf} after oral dose
V_z/F	Apparent volume of distribution after oral dose	Dose/(AUC_{inf}*k_{el}) after oral dose
T_{last}	The time for C_{last}	Observed directly from the data

The plasma PK parameters in Table 3 will be summarized descriptively by treatment, as applicable, in accordance with Pfizer data standards. Plasma concentrations will be listed and summarized descriptively by nominal PK sampling time and treatment. Individual participant and median profiles of the plasma concentration-time data will be plotted by treatment using actual and nominal times, respectively. Median profiles will be presented on both linear-linear and log-linear scales.

To estimate the relative BA of ritlecitinib (PF-06651600) pediatric capsule (3 × 10 mg capsules) relative to adult 30 mg capsule, the natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effects model with sequence, period and treatment as fixed effects and participant within sequence as a random effect. 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. Treatment A (30 mg capsule form of ritlecitinib [PF-06651600] under fasted conditions) will be the Reference treatment while Treatment B (3 × 10 mg pediatric capsules of ritlecitinib [PF-06651600] under fasted conditions) will be the Test treatment. Data from Period 3 (Treatment C) will be excluded from this analysis.

To estimate the relative BA of ritlecitinib (PF-06651600) administered as 30 mg spray congealed beads (Test) relative to adult 30 mg capsule (Reference) under fasted conditions, the natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effects model with sequence and treatment as fixed effects and participant within sequence as a random effect. 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. Treatment A (30 mg capsule of ritlecitinib

[PF-06651600] under fasted conditions) will be the Reference treatment while Treatment C (30 mg spray congealed beads of ritlecitinib [PF-06651600] under fasted conditions) will be the Test treatment.

9.4.4. Taste Assessment Analyses

The data used in the analysis will be transcribed and rescaled to a score from 0 to 100 from the raw measurements on the taste questionnaire. The sensory attributes (overall liking, mouth feel, bitterness, sourness, saltiness, tongue/mouth burn) from the taste assessment questionnaire (Appendix 9) for Treatment C (30 mg spray congealed beads) will be listed and descriptively summarized by collection time. Radar plots for each time point, summarizing all attributes, will be generated.

9.4.5. Other Analyses

Pharmacogenomic sample will be collected and retained for future analyses, but will not be analyzed, specifically, for this study.

9.5. Interim Analyses

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

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will not use a DMC.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant 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, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

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

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

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

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, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

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

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

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

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator

is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

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

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

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the IQMP.

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

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

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

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

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will

promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

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

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

Definition of what constitutes source data can be found in the Source Document Locator.

Description of the use of computerized system is documented in the Source Document Locator.

10.1.8. Study and Site Start and Closure

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

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

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of

the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submit all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer-intervention related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor’s Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the CTMS.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact

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

10.2. Appendix 2: Clinical Laboratory Tests

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

Table 4. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin	BUN and creatinine	pH	Urine drug screening[b]
Hematocrit	Glucose (fasting)	Glucose (qual)	Pregnancy test (β-hCG)[c]
RBC count	Calcium	Protein (qual)	**At Screening Only**
MCV	Sodium	Blood (qual)	FSH[d]
MCH	Potassium	Ketones	HBsAg[e]
MCHC	Chloride	Nitrites	HBcAb[e]
Platelet count	Total CO_2 (bicarbonate)	Leukocyte esterase	HCVAb[e]
WBC count	AST, ALT	Urobilinogen	HIV
Total neutrophils (Abs)	Total bilirubin	Urine bilirubin	QuantiFERON- TB Gold Test[f]
Eosinophils (Abs)	Alkaline phosphatase	Microscopy[a]	Lipid Panel[g]
Monocytes (Abs)	Uric acid		
Basophils (Abs)	Albumin		
Lymphocytes (Abs)	Total protein		
	CK[h]		
	eGFR (CKD-EPI [serum Creatinine based])		

a. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
b. At Screening and Admission. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).
c. Serum β-hCG for female participants of childbearing potential.
d. At Screening for confirmation of postmenopausal status only.
e. If HBsAg is negative and HBcAb is positive, HBsAb should be evaluated.
f. Complete at screening. Previous testing for QuantiFERON TB Gold Test will be accepted if completed within 12 weeks prior to screening. Otherwise should be completed at screening and results available prior to Day 1.
g. Lipid panel tests include LDL (calculated), HDL, triglycerides and total cholesterol, and require fasted conditions for at least 10 hours.
h. In addition to re-testing creatine kinase >3 × ULN, urine myoglobin will be performed as reflex testing for any participant with creatine kinase >10 × ULN.

Investigators must document their review of each laboratory safety report.

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

10.3.1. Definition of AE

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

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

Events NOT Meeting the AE Definition

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

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the CT SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must

be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

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

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.

- New or updated information will be recorded in the originally completed CRF.

- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.

- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.

- The site will enter the SAE data into the electronic system as soon as the data become available.

- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool

has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form

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

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

- No contraception methods are required for male participants in this study, as the calculated safety margin is ≥100-fold between the estimated maternal exposure due to seminal transfer of ritlecitinib (PF-06651600) and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies.

10.4.2. Female Participant Reproductive Inclusion Criteria

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

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

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described below, during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

- A WOCBP agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

10.4.3. Woman of Childbearing Potential

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

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

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

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;

- Documented bilateral salpingectomy;
- Documented bilateral oophorectomy.

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

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

2. Postmenopausal female.
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:
     - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.
     - A female on HRT and whose menopausal status is in doubt will be excluded from the study.

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.

Males

No contraception methods are required for male participants in the study.

Females

The following applies to female participants who are considered WOCBP.

Highly Effective Contraceptive Methods

1. Oral, injectable, or implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion or bilateral tubal ligation.

5. Oral, intravaginal, transdermal, or injectable combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation used in combination with a barrier method.

   Acceptable barrier methods include:

   - 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).

6. 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.

7. Sexual abstinence.

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

10.5. Appendix 5: Genetics

Use/Analysis of DNA

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

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

- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to ritlecitinib (PF-06651600) 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:

    - Samples for banking 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 Banked Biospecimens 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.

- Banked Biospecimens will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held at the study site and will not be provided to the sample bank.

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

Potential Cases of Drug-Induced Liver Injury

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

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy’s law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as AEs

- Marked sinus bradycardia (rate <40 bpm) lasting minutes.
- New PR interval prolongation >280 msec.
- New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline.
- New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm.
- New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration.
- Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.

ECG Findings That May Qualify as SAEs

- QTcF prolongation >500 msec.
- New ST-T changes suggestive of myocardial ischemia.
- New-onset left bundle branch block (QRS >120 msec).
- New-onset right bundle branch block (QRS >120 msec).
- Symptomatic bradycardia.
- Asystole:
  - In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.
  - In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.
  - Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (heart rate <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm (such as torsades de pointes)).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

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

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

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

These guidelines for participant safety monitoring and discontinuation are to be applied to all participants in Study B7981030. Additional individual participant monitoring is at the discretion of the investigator and dependent on any perceived safety concerns. Unscheduled clinical labs may be obtained at any time during the study to assess such concerns, and a participant may be withdrawn at any time at the discretion of the investigator.

10.8.1. Participant Safety Monitoring

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

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

The following laboratory abnormalities require retesting until resolution or agreement with Pfizer:

Laboratory Variable	Laboratory Value	Re-testing Timeframe
Hematology		
Absolute Neutrophil Count	$<1000/mm^3$ ($<1.0 \times 10^9/L$)	Within 48 hours
Hemoglobin	<10.0 g/dL (<6.21 mmol/L or <100 g/L) OR Decrease of ≥2.0 g/dL from baseline	Within 48 hours
Platelet count	$<100,000/mm^3$ ($<100.0 \times 10^9/L$)	Within 48 hours
Absolute Lymphocyte Count[a]	$<600/mm^3$ ($<0.6 \times 10^9/L$)	Within 48 hours
Serum Chemistry		
Creatine kinase[a]	>3 × ULN	Within 48 hours
Aspartate aminotransferase	See Section 10.6 Appendix 6 for potential cases of drug induced liver injury.	Within 48 hours
Alanine aminotransferase	See Section 10.6 Appendix 6 for potential cases of drug induced liver injury.	Within 48 hours
Total bilirubin	See Section 10.6 Appendix 6 for potential cases of drug induced liver injury.	Within 48 hours

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

10.8.2. Participant Discontinuation Criteria

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

Adverse Events:

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

ECG Abnormalities

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

Laboratory Abnormalities:

- All the following laboratory abnormalities require discontinuation if they are confirmed:
  - Absolute Neutrophil Count <750/mm^3 (<0.75 × 10^9/L);
  - Hemoglobin <9.0 g/dL (<5.59 mmol/L or <90 g/L) or a decrease of >30% from baseline (either criterion or both);
  - Platelet count <75,000/mm^3 (<75.0 × 10^9/L);
  - Absolute Lymphocyte Count <500/mm^3 (<0.5 × 10^9/L);
  - Creatine kinase >10 × ULN.

    NOTE: In addition to retesting creatine kinase >3 × ULN, urine myoglobin will be performed as reflex testing for any participant with creatine kinase >10 × ULN.
  - AST or ALT that meet ANY of the following:
    - >3 times ULN with at least one total bilirubin value >2 times ULN;
    - >3 times ULN accompanied by signs or symptoms consistent with hepatic injury (eg, new onset elevated PT/INR);

- Two sequential AST or ALT elevations >5 times ULN, regardless of total bilirubin or accompanying signs or symptoms.

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

10.9. Appendix 9: Taste Assessment Questionnaire

1. The questionnaire should be administered to adult participants, preferably by the trained staff. The clinical staff is trained by the CRU clinical coordinator for performing the taste assessment questionnaire and regarding the specific study restrictions.

2. Use a colored copy of the questionnaire.

3. Do not alter (reduce or enlarge) the original size of the questionnaire.

4. Participants will be asked as much as possible to not verbalize their responses and not discuss taste with other participants until after they have filled out the responses in the questionnaire.

5. Please collect the following background information:

Background Information

Study number / Study Site	
Study Period and Day	
Participant identification (ID) (Rand ID)	
Formulation ID	
Collection Date	
Collection Time	
Name of trained staff administering the questionnaire	
Questionnaire fully completed	Yes / No

Example: How to provide a mark (✕) on the color bar and how to calculate the score.

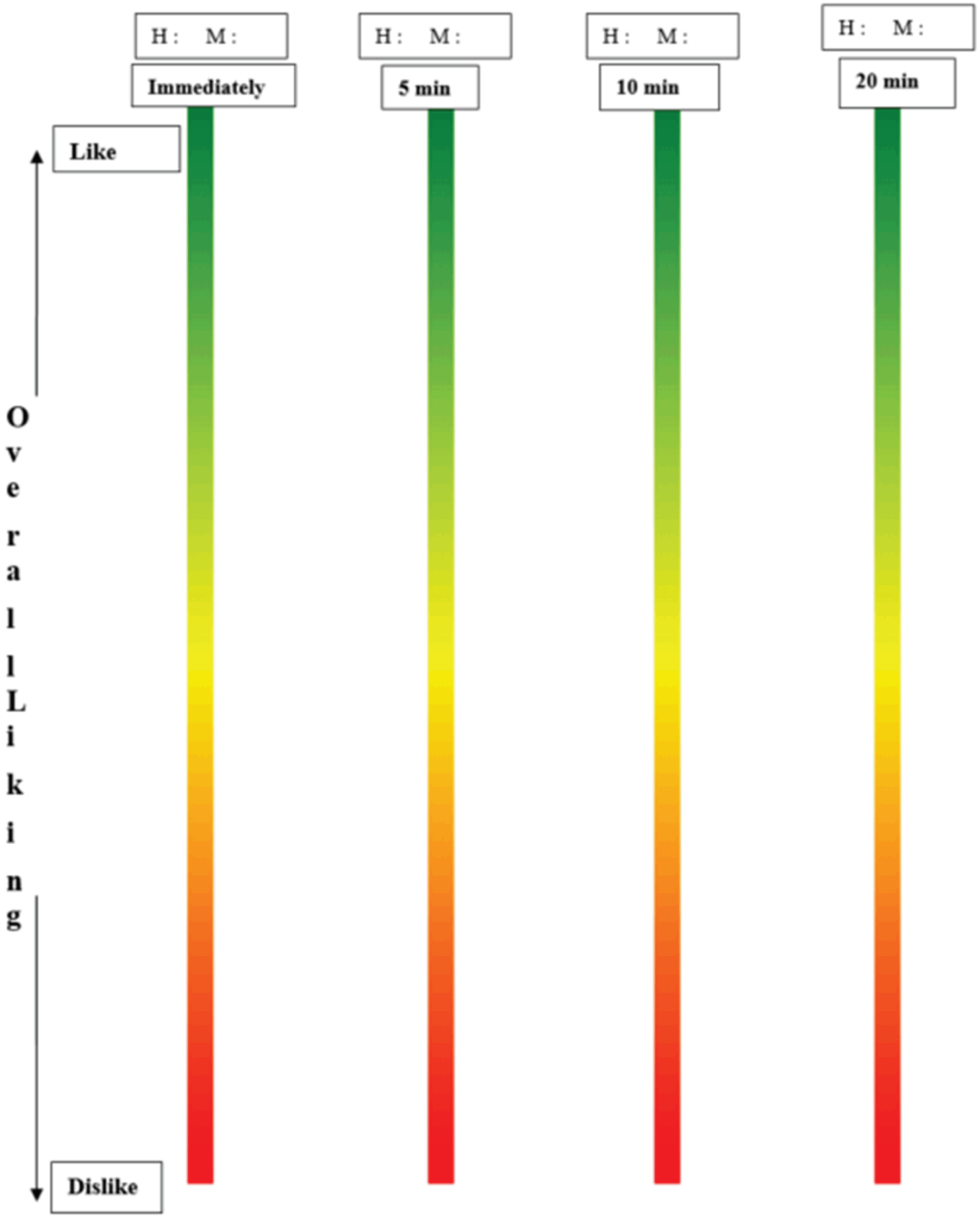
In visual analogue scores, the length of the bar might be different from page to page when printed off. Scores should be calculated as follows:

1. Measure the length of the bar on the printed page (for example 11 cm).
2. Measure the placement of the "X" (distance from the top of the bar) (for example 7 cm from the top).
3. Calculate the relative placement of the "X" (for example 7 cm/11 cm). This is the score.

This allows for a more accurate measurement of "X" regardless of the actual length of the bar on the printed page.

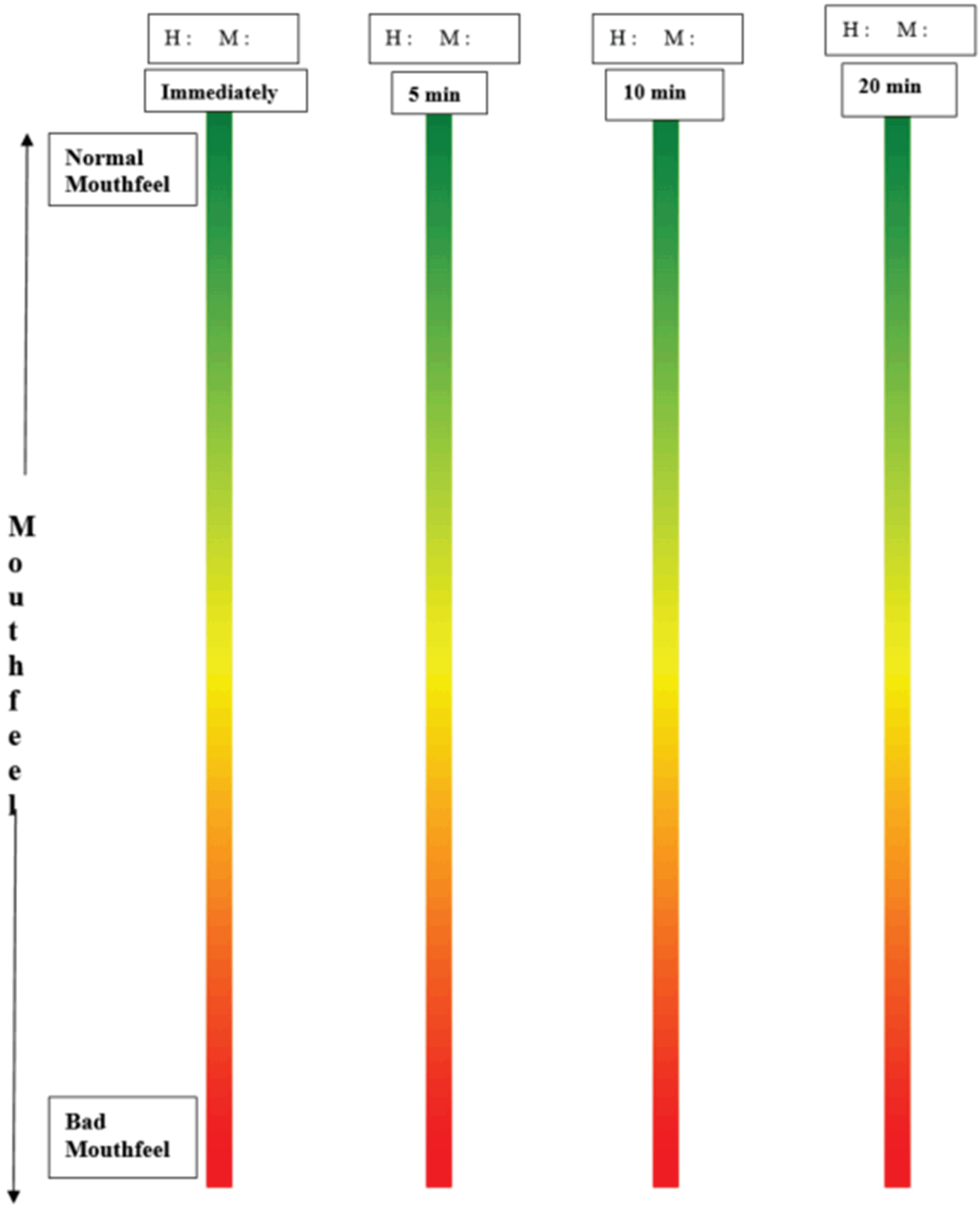
Questionnaire:

Q1. Overall Liking – please tell us how much you like or dislike the product you tasted by providing a mark (✕) on the color bar:



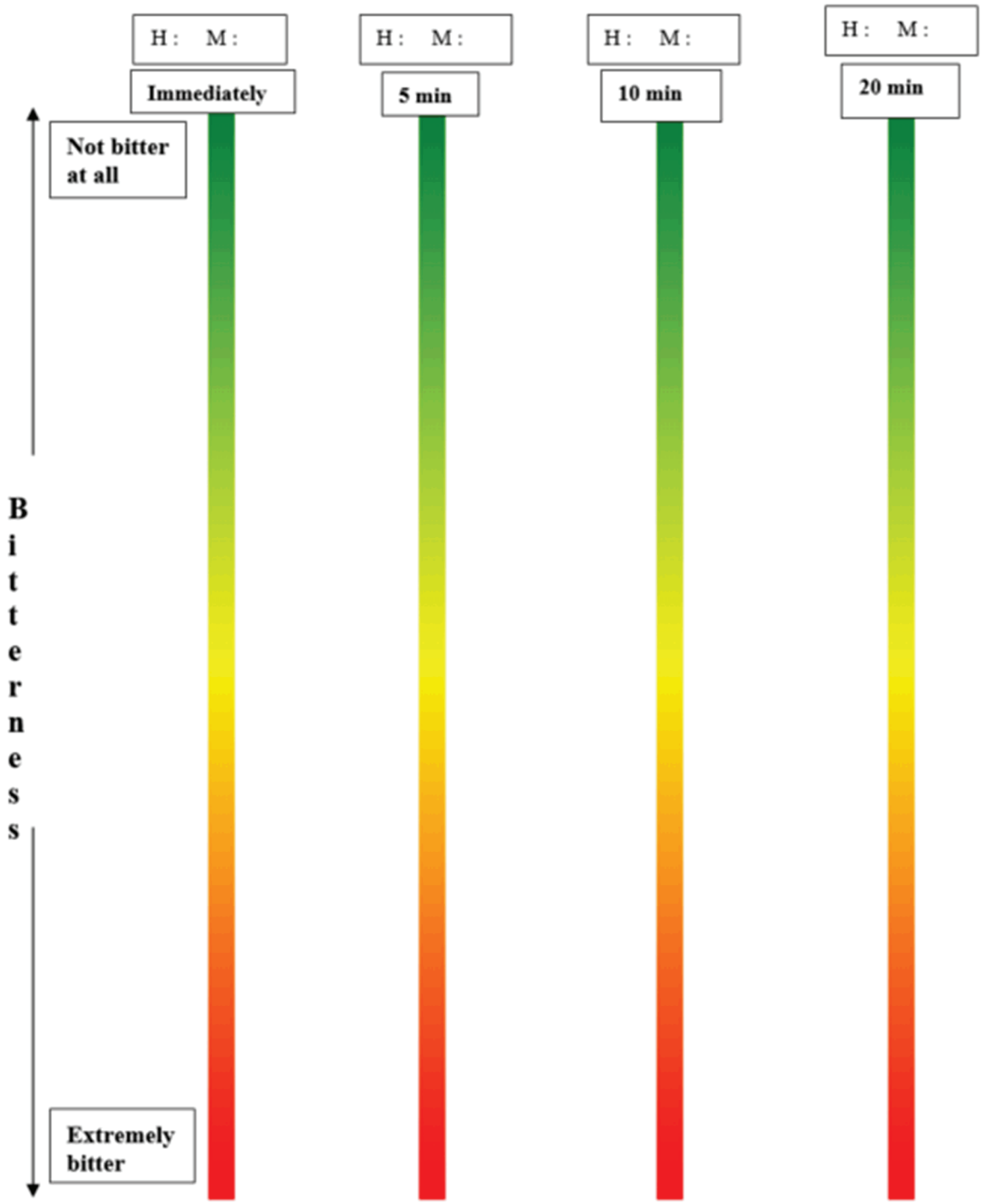
"**Immediately" refers to immediately after dosing**

Q2. Mouth feel – please tell us about the mouthfeel (such as grittiness, stickiness, waxiness) of the product you tasted by providing a mark (✕) on the color bar:



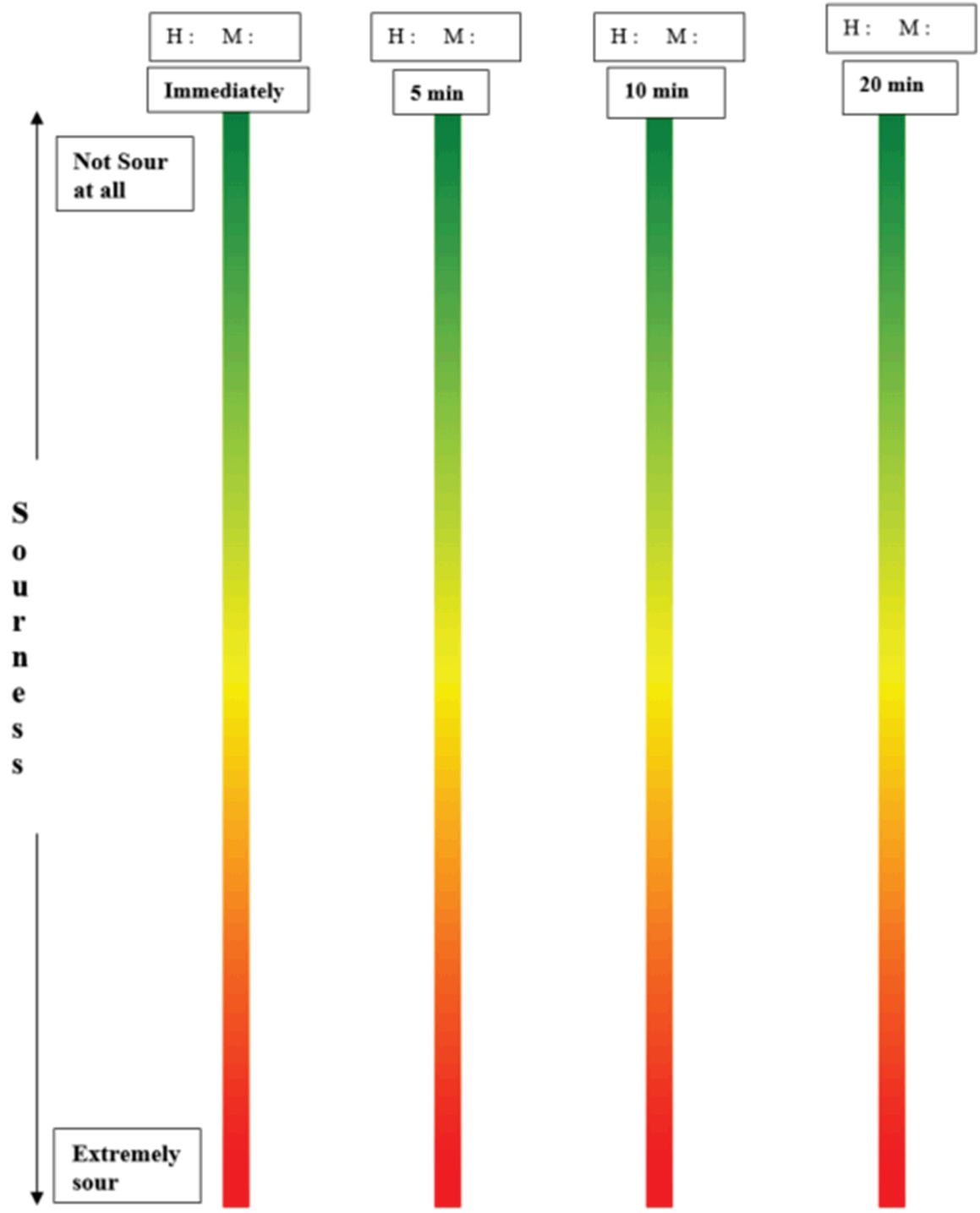
"**Immediately" refers to immediately after dosing**

Q3. Bitterness – please tell us about the degree of bitterness of the product you tasted by providing a mark (✕) on the color bar:



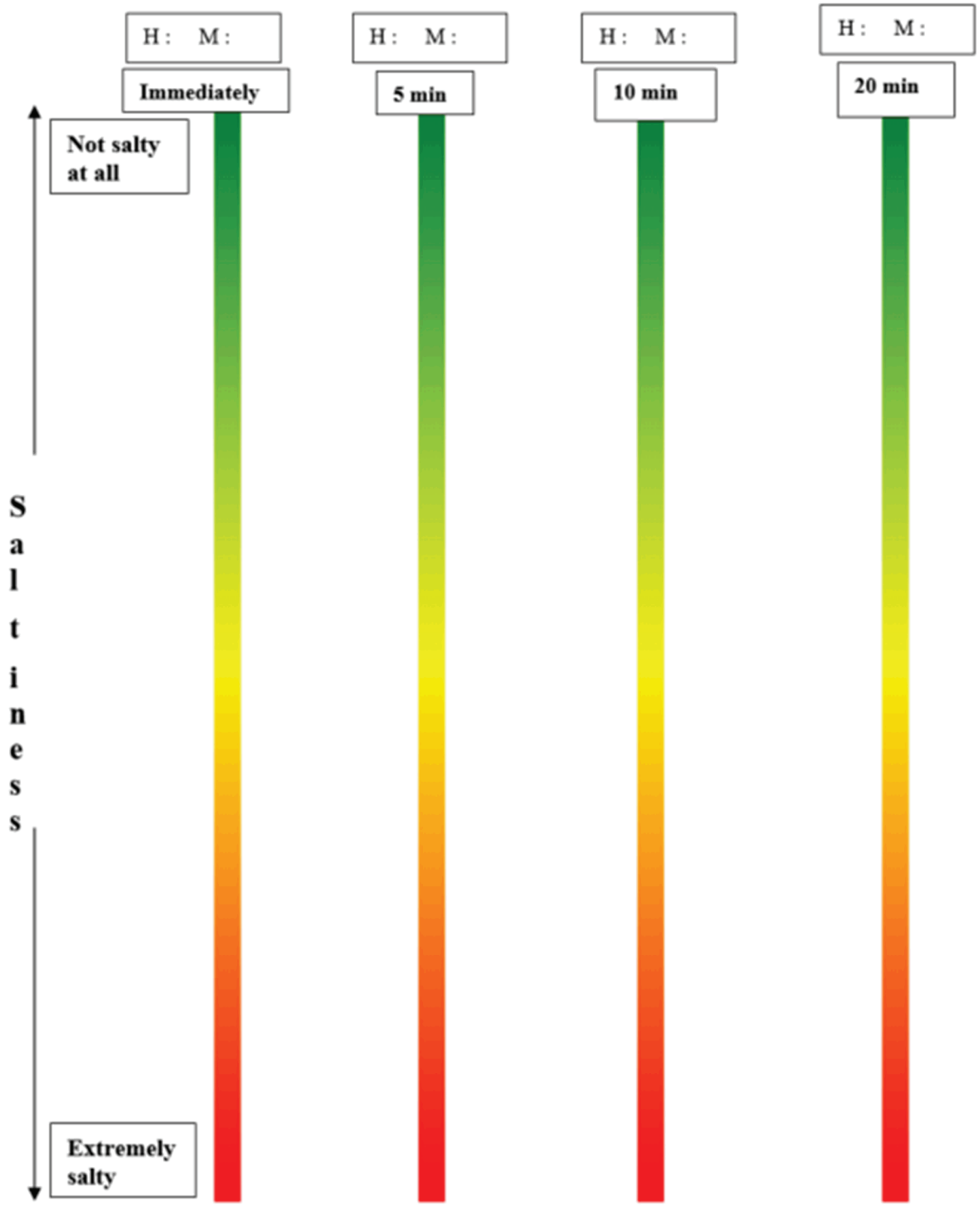
"**Immediately" refers to immediately after dosing**

Q4. Sourness – please tell us about the degree of Sourness of the product you tasted by providing a mark (✕) on the color bar:



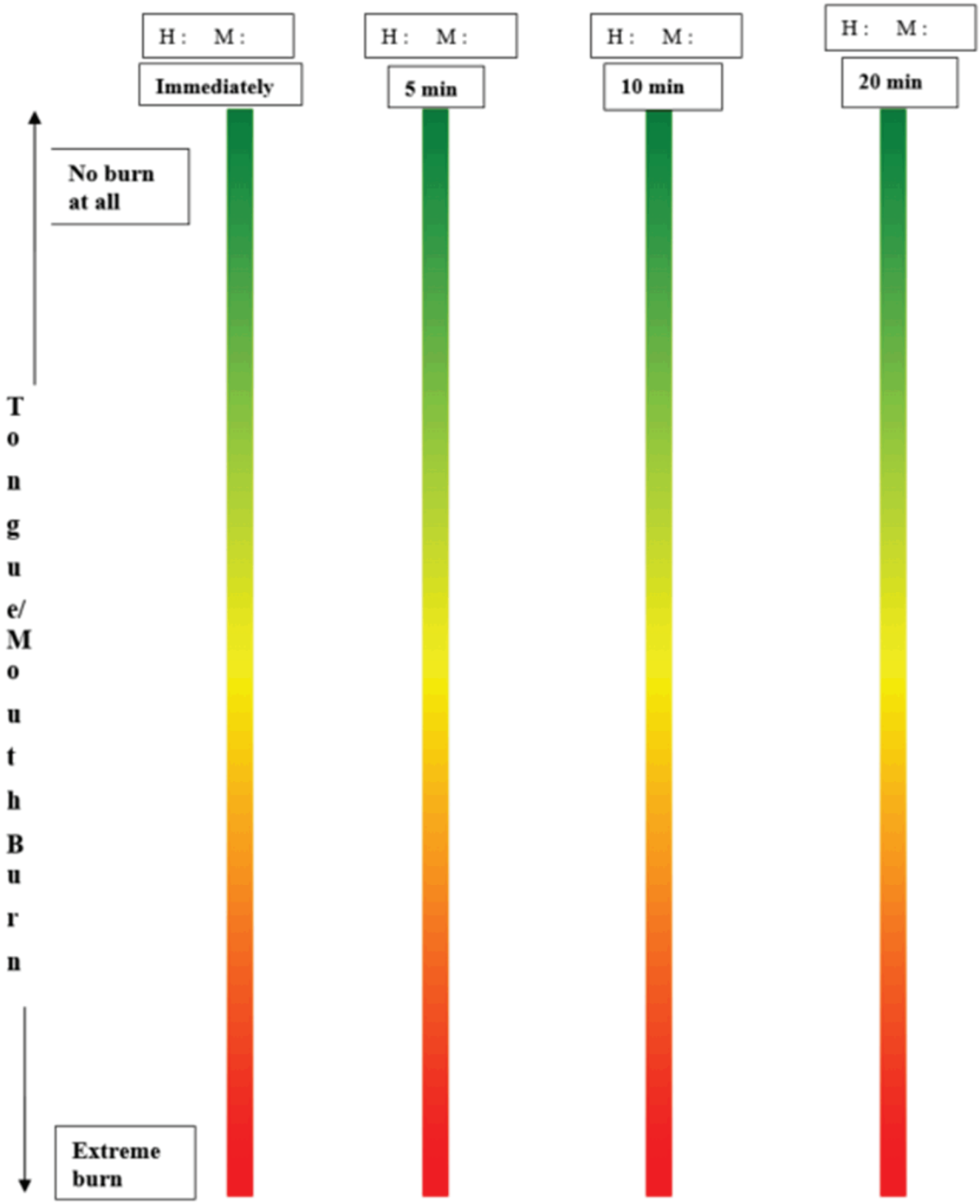
"Immediately" refers to immediately after dosing

Q5. Saltiness – please tell us about the degree of saltiness of the product you tasted by providing a mark (✕) <u>on the color bar</u>:



"**Immediately" refers to immediately after dosing**

Q6. Tongue/Mouth Burn – please tell us about the degree of tongue/mouth burn you experienced after you tasted the product by providing a mark (✕) on the color bar:



"**Immediately" refers to immediately after dosing**

10.10. Appendix 10: Abbreviations

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

Abbreviation	Term
AA	alopecia areata
Abs	absolute
AE	adverse event
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
BA	bioavailability
BE	bioequivalence
β-hCG	beta-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 Collaboration
C_{last}	last quantifiable concentration

Abbreviation	Term
CL/F	apparent clearance after oral dose
C_{max}	maximum plasma concentration
CO	Cross-Over
CO_2	carbon dioxide (bicarbonate)
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	clinical study report
CT	clinical trial
CTMS	clinical trial management system
DCT	data collection tool
DILI	drug induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
EBV	Epstein Barr Virus
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FIH	first in human
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma glutamyl transferase
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody

Abbreviation	Term
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HDL	high-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IL	interleukin
IND	investigational new drug
INR	international normalized ratio
IP	investigational product
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IQMP	Integrated Quality Management Plan
IRB	institutional review board
JAK	Janus kinase
k_{el}	terminal phase rate constant
LBBB	left bundle branch block
LDL	low-density lipoprotein
LFT	liver function test
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MMR	measles mumps rubella
msec	millisecond
N/A	not applicable

Abbreviation	Term
NOAEL	no-observed-adverse-effect level
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PPD	purified protein derivative
PT	prothrombin time
PVC	premature ventricular contraction/complex
QD	once daily
QFT-G	QuantiFERON®-TB Gold In-Tube
QRS	time from ECG Q wave to the end of the S wave corresponding to ventricle depolarization
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
RA	rheumatoid arthritis
RAND	randomization
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SBE	Single-Blind Extension
SCr	serum creatinine
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TBili	total bilirubin
TEAE	treatment-emergent adverse events
TEC	tyrosine kinase expressed in hepatocellular carcinoma
THC	tetrahydrocannabinol

Abbreviation	Term
T_{last}	The time for C_{last}
T_{max}	time for maximum plasma concentration
TYK	tyrosine kinase
$t_{½}$	terminal elimination half-life
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
V_z/F	apparent volume of distribution after oral dose
WBC	white blood cell
WOCBP	woman of childbearing potential

11. REFERENCES

1. Banholzer ML, Wandel C, Barrow P, et al. Clinical trial considerations on male contraception and collection of pregnancy information from female partner: update. Clin Transl Med 2016;5(1):23 37.