AN INTERVENTIONAL PK, PD, PHASE 1, OPEN-LABEL STUDY TO INVESTIGATE PK AND PD OF MULTIPLE-DOSE RITLECITINIB IN CHILDREN 6 TO LESS THAN 12 YEARS OF AGE WITH SEVERE ALOPECIA AREATA

Study Intervention Number:	PF-06651600
Study Intervention Name:	Ritlecitinib
US IND Number:	131503
EudraCT/CTIS Number:	NA
ClinicalTrials.gov ID:	NA
Pediatric Investigational Plan Number:	EMEA-002451-PIP01-18
Protocol Number:	B7981031
Phase:	1

Brief Title: An Open-Label, Multiple-Dose, PK, PD Study of Ritlecitinib in Children 6 to <12 Years of Age With Severe Alopecia Areata

Document History

Document	Version Date
Original protocol	03 Oct 2022

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: An Interventional PK, PD, Phase 1, Open-Label Study to Investigate PK and PD of Multiple-Dose Ritlecitinib in Children 6 to less than 12 Years of Age With Severe Alopecia Areata

Brief Title: An Open-Label, Multiple-Dose, PK, PD Study of Ritlecitinib in Children 6 to <12 Years of Age With Severe Alopecia Areata

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Protocol Number:	B7981031
Phase:	Phase 1

Rationale:

The PK assessments from this study are necessary to support ritlecitinib dose selection in subsequent studies in children aged 6 to <12 years of age.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary:	**Primary:**
• To characterize the PK of ritlecitinib in children with AA 6 to <12 years of age.	• AUC_{24} on Day 7
Secondary:	**Secondary:**
• To further characterize the PK of ritlecitinib in children with AA 6 to <12 years of age.	• C_{max}, T_{max}, CL/F, V_Z/F and $t_{½}$ on Day 7
• To characterize the PD of ritlecitinib in children with AA 6 to <12 years of age.	• Change from baseline in interferon gamma IP-10 and lymphocyte subsets (T cell, B cell, and NK cells) on Day 7
• To evaluate the safety and tolerability of ritlecitinib in children with AA 6 to <12 years of age.	• Treatment-emergent adverse events (AEs). • Treatment related AEs. • SAEs and AEs leading to discontinuation. • Clinically significant abnormalities in vital signs. • Clinically significant abnormalities in clinical laboratory values.
• To assess the overall palatability, acceptability, and tolerability of the proposed age appropriate formulation in children with AA aged 6 to <12 years of age.	• Taste assessment

Overall Design:

Study B7981031 is a single-group, uncontrolled, open-label, interventional PK, PD study to estimate the systemic exposures of 20 mg QD of ritlecitinib in at least 12 children with AA, 6 to <12 years of age, including at least 4 participants 6 to <9 years of age.

The dose to be studied was derived by allometric scaling of results obtained from adults and adolescents who received ritlecitinib. Participants in this study will receive ritlecitinib for 7 days, with PK, PD assessments on Day 7.

Number of Participants:

Twelve evaluable participants will be required to complete the PK analysis at Day 7. At sponsor's discretion, up to 3 participants may be replaced if they do not provide a full set of evaluable PK data.

Note: "Enrolled" means an agreement has been obtained of a participant and their legally authorized representative(s)to participate in a clinical study following completion of the informed consent process and assignment to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.

Study Population:

The full set of inclusion/exclusion criteria is provided in Section 5 of the protocol.

Key inclusion and exclusion criteria are listed below:

Key Inclusion Criteria

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

1. Children who are 6 to <12 years old at the time of the screening visit. Refer to (Section 10.4) for reproductive criteria for male and female participants.

2. A diagnosis of severe AA, including AT and AU, with ≥50% scalp hair loss due to AA (ie, a SALT score ≥50) at both the Screening and Baseline visits, without evidence of terminal hair regrowth within the previous 12 months.

3. For study participants in the EU/UK only:

   History of clinical response failure to AA treatment (such as topical, off-label pharmacologic, or hairpiece prosthetics)

AND EITHER:

a. Participants with a history of psychological counseling for AA (as evidenced by Screening AA assessments) in the past year prior to Screening

Participants are eligible if current psychosocial impairment is confirmed by administering all four instruments listed below and meeting the specified thresholds:

- PROMIS® Parent Proxy Anxiety Symptoms: T-score 60-70
- PROMIS® Parent Proxy Depressive Symptoms: T-score 60-70
- BRIEF®2 (BRI, ERI, CRI): T-score 60-70 on any one of the 3 components of the BRIEF®2.
- Modified CDLQI (score of ≥7)

OR

b. Participants with no history of psychological counseling for AA in the past year prior to Screening

In order to be eligible for this study, participants must:

- Have a T-score of 60-70 on any one of the 3 instruments (PROMIS®Anxiety Symptoms or PROMIS®-Depressive Symptoms or any one of the 3 components of BRIEF®2)
- Complete at least 5 psychological counseling sessions for AA prior to Screening
- Be re-evaluated after completion of the psychological counseling and have a T-score of 60-70 on any one of the three instruments (PROMIS®Anxiety- Symptoms or PROMIS®-Depressive Symptoms or any one of the 3 components of BRIEF®2)

Key Exclusion Criteria

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

1. Conditions that may impact absorption or metabolism of IP (eg, celiac disease, cholecystectomy or gastrectomy).
2. History (one or more episodes) of CMV, varicella, herpes zoster (shingles) or disseminated herpes simplex. A history of uncomplicated herpes simplex is not exclusionary.

3. Other medical or psychiatric condition (including recent [within the past year] or active suicidal ideation/behavior) that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study, including but not limited to:

   - For participants in the EU/UK with scores of >70 on the PROMIS® or any component of the BRIEF®2, or with previous history of suicidal behaviors in the past 5 years, "Yes" answer for events that occurred in the past 5 years to any of the suicidal behavior items of the C-SSRS or with any lifetime history of serious or recurrent suicidal behavior, a risk assessment must be performed and documented by a qualified mental health professional to assess whether it is safe to participate in the trial.

   - For participants in the US and other non-EU/UK countries with a previous history of suicidal behaviors in the past 5 years, "Yes" answer for events that occurred in the past 5 years to any of the suicidal behavior items of the C-SSRS or with any lifetime history of serious or recurrent suicidal behavior, a risk assessment must be performed and documented by a qualified mental health professional to assess whether it is safe to participate in the trial.

   - For participants in the US and other non-EU/UK countries: Clinically significant depression per the CDRS-R (T-score ≥40).

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

4. Renal dysfunction defined as:

   - eCrCl normalized to BSA: confirmed eCrCl <60 mL/min/1.73 m^2 based on Modified Schwartz equation (pediatric patients 2 to <12 years of age). See Appendix 6.

5. Hepatic dysfunction defined as:

   - Total bilirubin >1.5 × ULN (except for Gilbert's syndrome)

   - AST >1.5 × ULN

   - ALT >1.5 × ULN

6. Hematologic abnormalities defined as:

   - Absolute neutrophil count <1.2 × 10^9/L (<1200/mm^3)

   - Hemoglobin <11.0 g/dL

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

- Absolute lymphocyte count of $<0.8 \times 10^9$ /L ($<800/mm^3$)

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

Study Arms and Duration:

The study includes a screening period of up to 28 days, a 7-day interventional period, and a 28 day follow-up period. The duration of study participation for each participant is approximately 9 weeks.

Study Intervention(s)	
Intervention Name	Ritlecitinib (PF-06651600)
Arm Name (group of participants receiving a specific treatment or no treatment)	Active study medication
Unit Dose Strength(s)	20 mg
Route of Administration	Oral
Use	Experimental
IMP or NIMP/AxMP	IMP

Arm Title	experimental
Arm Type	experimental
Arm Description	Participants will receive study medication, 20 mg per day, for 7 days.

Statistical Methods:

A sample size of 12 participants should provide adequate pharmacokinetic information. The plasma PK parameters will be listed and summarized descriptively. Plasma concentrations will be listed and summarized descriptively by nominal PK sampling time. Individual participant and median profiles of the plasma concentration-time data will be plotted using actual and nominal times, respectively. Median profiles will be presented on both linear-linear and log-linear scales.

Taste acceptability assessment questionnaire will be included. Taste acceptability will be listed and summarized descriptively (frequencies and percentages).

Ethical Considerations:

As of August 2022, there are no systemic treatments approved by Health Authorities for the treatment of AA in pediatric patients.

Review of the treatment guidelines and recommendations indicates that a number of off-label therapies are frequently used after assessing factors such as the age of the patient, disease extent and disease duration. However, there is neither a cure for AA nor is there a therapy convincingly demonstrated to induce and sustain drug-free remission long term. [1,2,3,4,5] Most recently, JAK inhibitors have been studied in AA and encouraging reports regarding their efficacy have been published and presented. [6,7,8]

The results of previous studies of ritlecitinib in adults and adolescents support the investigation of ritlecitinib for AA in children and there is a favorable benefit-risk profile to support the rationale for this study. Taking into account the measures to minimize risk to participants, the potential risks associated with ritlecitinib are justified by the anticipated benefits of informing dose selection in studies evaluating ritlecitinib for the treatment of AA in children.

This is a short-term PK, PD study and therefore no benefit to the participants is expected. However, participants who complete this study will qualify to be screened for a planned long-term, open-label study, where ritlecitinib (active dose only) will be provided for up to 3 years. Dose selection for this planned study will be based on results from Study B7981031, and thus enrollment into the planned long-term study will not occur immediately after Study B7981031.

The clinical data from the B7981015 study of ritlecitinib in adults and adolescents (≥ 12 to <18 years of age) with AA indicate that ritlecitinib has a favorable benefit/risk profile for treatment of adults and adolescents with AA for up to 48 weeks. It provides meaningful clinical benefit in this serious disease with no approved treatment options in pediatric populations, and it has an acceptable safety profile. The benefit of evaluating ritlecitinib in children is additionally supported by the prevalence of AA in children and the significant psychological burden of AA in this population.

Participants and their parents/legal guardians will be expected to commit time for participating in this study as they will be required to visit the study site 3 times during the study (Screening, Day 1 and Day 7). Day 7 PK assessments will occur over an 8-hour period. Also, participants may experience some discomfort while undergoing study assessments such as blood draws.

Blood samples will be collected at Screening and Day 7 as follows:

Study Visit	Test	Screening	EOT
Screening	Hematology	0.5 ml	0.5 ml
	Blood chemistry	0.5 ml	0.5 ml
	QFT	1 ml	
	IP-10	1 ml	1 ml
	Lymphocyte subsets	2 ml	2 ml
	Hepatitis B/C	2 ml	
	HIV	2 ml	
	Pregnancy (serum)	2 ml	
Day 7	PK		5 ml (5 × 1 ml)
Total Blood Volume		11 ml	9 ml

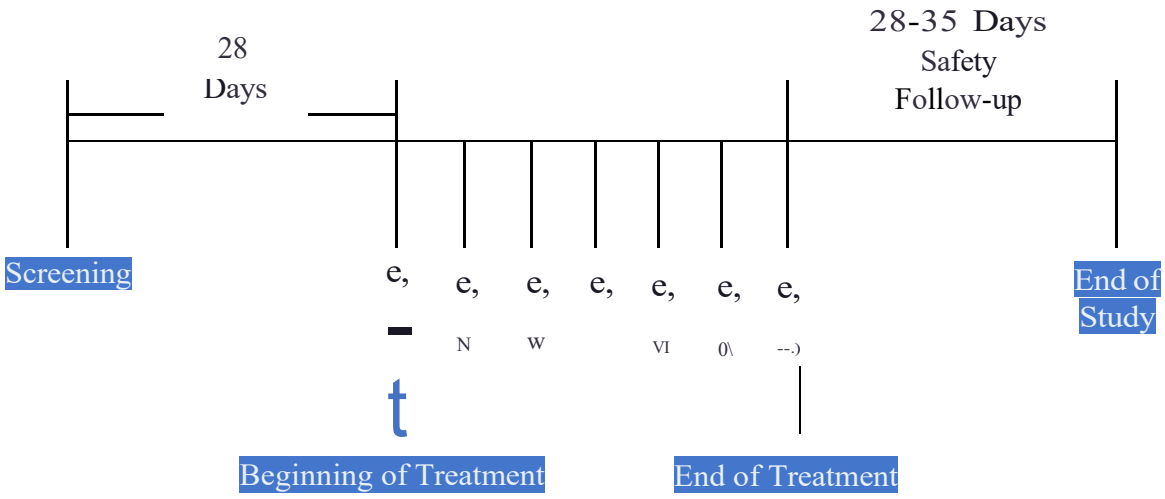
Additional blood tests may be required for safety reasons, as determined by the Investigator. The total amount of blood must be within the allowed limits for this patient population (see Section 8.1 for details).

In addition, participants must agree to use appropriate contraception methods if applicable, not use prohibited medications, and to follow protocol specified lifestyle guidelines during the study (see Appendix 4 and Appendix 7 for details).

The study incorporates mitigations against known risks to ensure the safety of the trial participants.

1.2. Schema

Figure 1. Study Visits and Procedures



Visit Types:

- Office visits: Screening, Day 1 (Beginning of treatment), Day 7 (End of Treatment) or Early Tennination
- Telephone visits: Days 2, 4, 6 and End of Study
- Optional home visits or additional office visits are allowed based on discretion of study site personnel and pai1icipant/legal guardian if considered necessaiy for dosing or safety issues
- PK draws: Day 7 (End of Treatment) or Early Temlination at Ohr (pre-dose), 0.5 hr, 1 hr, 3 hrs, and 8 hrs after dosing.

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 infonnation 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 paiiicipant. These visits may be conducted in the clinic, by telephone, or in the paiiicipant's home.

Visit Identifier Abbreviations used in this table may be found in Aooendix 17	**Sc1·een**	**T1·eatment Period**							**F/U End of Study**	**Notes**
	Up to 28 days before Day 1	**Day 1 Base line**	**Day** 2	**Day** 3	**Day 4**	**Day** 5	**Day 6**	**Day7 EOT**	**Day 35 to 42**	• Day relative to strut of study intervention (Day **1).** • F/U contact may occur via telephone and must occur 28 to 35 days after administration of the final dose of study intervention. • If treatment is discontinued prior to Day 7, an EOT visit must be conducted, followed by an End of Study visit at 28-35 days after the last dose. • If paiticipation in the study and treatment ai·e discontinued at the saine time, the EOT and EOS visits will be conducted together. • All screening should be done <28 davs before the first dose.
In-office visits	**X**	**X**						**X**		• In addition to specified in-office and telephone visits, additional in-office, telephone or in-home visits may be conducted at any time during the study for safety reasons or for reasons related to dosing or PK, PD blood draws.
Telephone visits			**X**		**X**		**X**		**X**	
Informed consent/assent	**X**									• Infonned consent and pa1ticipant assent should be obtained prior to undergoing any study-specific procedures.
Screen for inclusion/exclusion criteria	**X**									
Demographics	**X**									
Registration/ drug assiIDunent		**X**								At registration, the pa1ticipant enrollment number and treatment allocation are assiQtled.
Medical Histon and Phvsical Examination										
Medical history	**X**									
Full physical examination	**X**									

Visit Identifier Abbreviations used in this table may be found in Annendix 17	**Screen**	**T1·eatment Period**							**F/U End of Study**	**Notes**
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Brief physical examination		**X**						**X**		
Weillht/Heillht	**X**									
Vital siQtls	**X**							**X**		heart rate, blood pressure
Contraception check (if aoolicable)	**X**	**X**						**X**		
Laborntory Assessments										
Hematolo2v	**X**							**X**		
Blood chemistry	**X**							**X**		
QFT , Hepatitis B and C,HIV	**X**									
Urine dipstick	**X**									Urinalysis will be perfonned by dipstick in the clinic and the result documented at the site level (source document) ; if an abnonnal or symptomatic result is observed, the sample will be sent to the local laboratory. Microscopic analysis and urine culture will be performed if suspicion ofUTI and urinalysis is !Positive for nitrite and/or leukocyte esterase or if otherv.•ise clinically indicated.
Pregnancy test	**X**	**X**						**X**		Required only in females of childbearing potential. Semm at screening, urine at baseline and EOT. See Section 8.3.4 for additional info1mation)
Study Inte1-vention and Other Treatments										
Study medication intervention administration		**X**	**X**	**X**	**X**	**X**	**X**	**X**		
Prior/concomitant treatment(s)	**X**	**X**	**X**		**X**		**X**	**X**	**X**	

Visit Identifier Abbreviations used in this table may be found in Annendix 17	**Screen**	**T1·eatment Period**							**F/U End of Study**	**Notes**
	Up to 28 days before Day 1	**Day 1 Base line**	**Day** 2	**Day** 3	**Day 4**	**Day 5**	**Day 6**	**Day7 EOT**	**Day 35 to 42**	• Day relative to strut of study intervention (Day **1).** • F/U contact may occm via telephone and must occur 28 to 35 days after administration of the final dose of study intervention. • If treatment is discontinued prior to Day 7, an EOT visit must be conducted, followed by an End of Study visit at 28-35 days after the last dose. • If paiticipation in the study and treatment ai·e discontinued at the saine time, the EOT and EOS visits will be conducted together. • All screening should be done <28 days before the first dose.
Assessments										
SALT score	**X**	**X**								
Taste Assessment Questionnaire								**X**		
Serious and nonserious AE monitoring	**X**	**X**	**X**		**X**		**X**	**X**	X	
C-SSRS suicidal ideation and behavior risk assessment	**X**									
CDRS-R	**X**									US and other non-EU/UK countries
PROMIS® Pai·ent Proxy	**X**									EU/UK only
BRIEF®2 (BRI, ERi, CRI)	**X**									EU/UK only
Modified CDLOI	**X**									EU/UKonlv
WISC-V (Wechsler Intelligence Scale for Children - 5th edition)		**X**								EU/UK only
Documentation of psychological counseling	**X**									EU/UK only
Phannacokinetic Assessments										See laboratory manual.

Visit Identifier Abbreviations used in this table may be found in Annendix I7	**Screen**	**T1·eatment Period**							**F/U End of Study**	**Notes**
	Up to 28 days before Day 1	**Day 1 Base line**	**Day** 2	**Day** 3	**Day 4**	**Day 5**	**Day 6**	**Day7 EOT**	**Day 35 to 42**	• Day relative to strut of study intervention (Day **1).** • F/U contact may occm via telephone and must occur 28 to 35 days after administration of the final dose of study intervention. • If treatment is discontinued prior to Day 7, an EOT visit must be conducted, followed by an End of Study visit at 28-35 days after the last dose. • If paiticipation in the study and treatment ai·e discontinued at the saine time, the EOT and EOS visits will be conducted together. • All screening should be done <28 davs before the first dose.
PK samples								X		• PK samples required at Day 7 at Ohr (pre-dose), and 0.5 hr, 1 hr, 3 hrs, and 8 hrs after dosing. • PK will be conducted only on Day 7 and only if no more than one dose was missed between Davs 2 and 5.
										•
Phannacodvnamic assessments										
IP-10	**X**							**X**		• To be collected before dose. • IP-10 will be collected at screening and Day 7 only. If treatment is discontinued, IP-10 will not be collected on Dav 7.
Lymphocyte subsets (T cells, B cells, and NK cells)	**X**							**X**		• Lymphocyte subsets will be collected at screening and Day 7 only. If treatment is discontinued, lymphocyte subsets will not be collected at Day 7.

2. INTRODUCTION

2.1. Study Rationale

The PK and PD assessments from this study are necessary to support ritlecitinib dose selection in subsequent studies in children 6 to <12 years of age.

2.2. Background

AA is a chronic relapsing T-cell mediated autoimmune disorder characterized by non-scarring hair loss affecting children and adults across all ages, races, and sexes.[9,10] AA is associated with other immune diseases including asthma, allergic rhinitis, atopic dermatitis, and autoimmune diseases such as thyroiditis and vitiligo.[10]

$CD8^+$ T cells, NK cells, and mast cells are involved in the pathogenesis of AA. The possible inflammatory pathways in AA include cytokines from the TH1 axis, including IFN α, IFN γ, and IFNγ -IP-10.[11,12] Mouse models have shown that IL-2 and IL-15 play a role in the initiation of auto-reactive $CD8^+$ cells that attack hair follicles.[13] IL-12 and IL-23 may also play a role in the pathogenesis of AA.

Clinical presentation of AA can be limited to small, circular patches of scalp hair loss (patchy hair loss, alopecia focalis), involve complete loss of hair on the scalp (AT), or total loss of hair on the scalp and body (AU). AA involving 50% or greater scalp hair loss, including AT and AU, is considered an advanced form of alopecia, according to the US National Alopecia Areata Foundation.[14] Patchy alopecia is the most common form of AA which may develop into the more extensive and often treatment-resistant forms of AA, especially with earlier age of onset.[15] It is estimated that AA affects as many as 6 to 7 million individuals in the US[10] and 147 million worldwide.[14]

The spontaneous remission rates for AA patients presenting with <50% scalp hair loss (patchy hair loss, alopecia focalis) are 30-50% within the first 6-12 months of disease onset, and 66% of the patients will show complete regrowth of hair within 5 years.[16] The likelihood of complete regrowth spontaneously with AT or AU is less than 10%.[17]

Further, there is evidence that AA can become refractory to JAK inhibition if it has been present for a substantial period of time. Specifically, a recent case series demonstrated that AA patients whose current episode of alopecia totalis or alopecia universalis had lasted more than 10 years were highly non-responsive to off-label tofacitinib treatment in comparison with patients with shorter duration.[8]

Depression, anxiety, and panic disorders are often observed in patients with AA and the coping mechanisms of AA patients mirror those of grief and bereavement.[18,19] A substantial body of evidence demonstrates a widespread impact of AA on the psychological health of both adult and pediatric patients with AA, including impairment in self-esteem, increased incidence of anxiety and depressive disorders and other psychological conditions,[20,21,22,23,24] problems with social relations,[25] decreased HRQoL and QoL, as well as the QoL of their families.[26,27,28,29,30,31,32,33,34]

AA is a disease with significant pediatric prevalence, in addition to the burden of disease seen in adults, and ample evidence is available on the impact of AA on the mental health of adolescent patients. In a US study, children with AA had more psychological problems than those without AA. Specifically, those with AA exhibited more anxiety, depression, tendencies to withdraw, aggression, and delinquency. In addition, children with AA were more likely to exhibit somatic problems as well as problems in social relations and in attention span. Girls with AA seem to have been affected more in dimensions of total problems, anxiety/depression, and internalizing/externalizing syndromes. Children with AA were also less likely to have experienced positive life events in the year prior to exhibiting AA signs.[25]

In addition to experiencing a significant mental health burden, children with AA report experiencing other negative impacts to their QoL. Specifically, 75% of children aged 15-19 years reported instances of effects on QoL, 50% reported that the disease limited their participation in activities, 40% reported instances of bullying, and 35% reported that others noticed and commented on their condition. Rates of decrement in QoL, limitations on participation in activities, and bullying were heightened in older children aged 15-19 years compared to younger children.[35]

Given the finding that complete scalp hair loss with duration >10 years in adults is less likely to respond to treatment, pursuing treatment, even if only intermittently, in adolescents or even younger patients with stable, severe AA may prevent future irreversible hair loss.[8] Additionally, an earlier age of first onset has been reported to correspond to an increased lifetime risk of extensive disease. Differences in treatment responses are not expected for adolescent versus adult AA patients as suggested in 2 reports of tofacitinib (off-label use). [8,36] No meaningful differences were observed between treatment responses in adults and adolescents treated with ritlecitinib in Study B7981015 (reference Pfizer data on file).

As of August 2022, there are no systemic treatments approved by Health Authorities for the treatment of AA in pediatric patients.

Review of the treatment guidelines and recommendations indicates that a number of off-label therapies are frequently used after assessing factors such as the age of the patient, disease extent, and disease duration. However, there is neither a cure for AA, nor is there a therapy convincingly demonstrated to induce and sustain drug-free remission long term.[1-5]

Previous studies (B7981015 and B7981032) included adult and pediatric populations between ages of 12 to <18 years.

This study is specifically designed to collect data supporting a dose selection for pediatric patients 6 to <12 years of age.

2.2.1. Clinical Overview of Ritlecitinib

The ritlecitinib AA clinical development program was designed to evaluate the efficacy and safety of ritlecitinib treatment in adolescent (12 to <18 years of age) and adult (≥18 years of age) AA patients with ≥50% scalp hair loss (as assessed by SALT), including AT and AU.

The clinical development program of ritlecitinib in AA was a global program including 21 Phase 1 studies, 4 Phase 2/3 studies in AA and 1 Phase 2b study in vitiligo. The study in vitiligo is relevant for the evaluation of safety in AA due to similarities between the AA and vitiligo populations (including disease pathophysiology, age distribution, comorbidities), similar ritlecitinib dosing regimens to those in the AA studies, and similar safety monitoring in vitiligo and AA study protocols.

As of 30 May 2022, ritlecitinib had been orally administered to 1630 participants in these 5 Phase 2/3 clinical efficacy and safety studies, as follows: B7931005 (Phase 2a in AA), B7981015 (Phase 2b/3 in AA), B7981037 (Phase 2a AA study to provide additional data regarding the clinical relevance of the axonal dystrophy finding in the 9-month dog toxicity study), B7981032 (Phase 3 long-term safety study in AA), and B7981019 in vitiligo.

2.2.1.1. Pharmacokinetic Overview of Ritlecitinib

The PK profile of ritlecitinib is characterized by rapid absorption, rapid elimination ($t_{½}$ of ~2 hours) and is 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 beyond Day 6. Ritlecitinib has been evaluated at single oral doses ranging from 5 mg to 800 mg and multiple oral doses ranging from 50 mg to 400 mg QD and at 100 mg and 200 mg BID for 14 days. The clearance mechanisms for ritlecitinib in humans appear to be primarily by metabolism. Less than 10% of ritlecitinib is excreted unchanged in the urine.

2.2.1.2. Safety of Ritlecitinib in Adult and Adolescent Participants With AA (Study B7931015)

B7981015 was a Phase 2b/3, randomized, double blind, placebo controlled, dose ranging study to investigate ritlecitinib in both adolescent (≥12 to <18 years old) and adult (≥18 years old) participants with ≥50% scalp hair loss due to AA. The study had a maximum duration of approximately 57 weeks. This included an up to 5-week Screening period, a 48-week treatment period, and a 4-week follow up period. The treatment period was comprised of a placebo-controlled period that included a 4-week loading phase and a 20-week maintenance phase, followed by a 24-week extension phase.

Eligible participants were randomized to blinded ritlecitinib and matching placebo in a 2:2:2:2:1:1:1 (200 mg/50 mg, 200 mg/30 mg, 50 mg, 30 mg, 10 mg, placebo-200 mg/50 mg, and placebo-50 mg, respectively) manner for a total of 7 treatment sequences.

The study randomized 105 adolescents (12 to 17 years of age) and the distribution of adolescents across treatment groups was similar.

Ritlecitinib 200/50 mg, 200/30 mg, 50 mg and 30 mg were significantly superior to placebo at Week 24 on clinician-assessed and patient-reported endpoints related to scalp hair regrowth (including response based on absolute SALT ≤20, response based on absolute SALT ≤10, and PGI-C response). Exposure response modelling based on SALT ≤20 and SALT ≤10 response at Week 24 showed a positive relationship between dose and response. Ritlecitinib 200/50 mg, 200/30 mg, 50 mg and 30 mg were also nominally superior to placebo at Week 24 in producing improvement in eyebrows and eyelashes. Continued improvement in efficacy endpoints was seen between Week 24 and Week 48.

Overall efficacy was similar in adolescents (12 to <18 years of age) and adults (≥18 years of age).

The proportion of participants who experienced all-causality TEAEs was similar across treatment groups up to Week 24 (placebo-controlled period) and up to Week 48 (overall). The most frequently reported TEAEs in any group included nasopharyngitis, headache, and upper respiratory tract infection. Up to week 24, the incidence of nasopharyngitis, folliculitis, urticaria, dizziness, upper respiratory tract infection and urinary tract infection was higher in participants treated with ritlecitinib (particularly 200/50 mg and 200/30 mg) than placebo. Most TEAEs were mild to moderate in severity. Fourteen participants experienced 16 SAEs up to Week 48:

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

Of the 16 SAEs, 12 were considered by the investigator as unrelated to study intervention. The 4 SAEs that were considered related to study intervention in the opinion of the investigator were sepsis and empyema (both in 1 participant); breast cancer; and eczema. There were no deaths in the study.

Treatment with ritlecitinib was associated with changes in hematological parameters, some of which were dose dependent. In the first weeks of the study, there were slight, transient decreases in hemoglobin and small, variable changes in neutrophil and leukocyte levels. Small, early decreases in platelets were observed with ritlecitinib treatment; these levels remained stable up to Week 48. Dose-dependent early decreases in absolute lymphocyte levels, CD3 (T lymphocytes) and T lymphocyte subsets (CD4 and CD8) were observed. There was a dose-dependent early decrease in CD16/56 (NK cells), particularly in groups who had received a 200 mg loading dose of PF-06651600 for 4 weeks. Overall, there were no clinically meaningful effects of ritlecitinib on ALT, AST, bilirubin, or alkaline phosphatase. The incidence of elevation in hepatic enzymes was low and not dose dependent. Up to Week 48, there were no potential Hy's law cases.

Overall, ritlecitinib was safe and well-tolerated in the adolescent population. In general, there was a lower proportion of adolescent participants with SAEs, severe AEs and AEs of interest relative to adult (≥18 years of age) participants. The TEAEs suggest there are no risks unique to adolescents, except for a higher frequency of acne in the adolescent patients which is not unexpected considering that acne is generally more common in adolescents than adults.

For a complete description and results of this study, please refer to the current version of the ritlecitinib IB.

2.3. Benefit/Risk Assessment

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

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) Ritlecitinib		
• viral reactivation • serious infections and opportunistic infections • malignancy and lymphoproliferative disorders • thromboembolism • dermatologic effects (eg. rash, acne, folliculitis, urticaria) • reduction in platelet count and lymphocyte count	Clinical experience with other JAK inhibitors Ritlecitinib clinical studies (B7931005, B7981015, B7981019, B7981032, and B7981037) and pre-clinical studies	Exclusion of participants at risk Short duration of treatment Safety labs at screening, baseline and EOT Visit
Study Procedures blood collection for PK		
Extravasation, bruising, local discomfort	Collection of 5 PK samples on Day 7	Use of highly qualified pediatric nurses, with venipuncture experience. When possible, use of IV canula, allowing all 5 samples to be collected with just one venipuncture.

2.3.2. Benefit Assessment

No immediate therapeutic benefits are expected from participation in this study. However, after completion of this study, participants will qualify to be screened for the planned 3-year, long-term, open-label (active dose only) Study B7981028. Dose selection for this planned study will be based on results from Study B7981031, and thus enrollment into the planned long-term study will not occur immediately after Study B7981031. Also, data collected in this study will support dose selection for the planned pediatric safety and efficacy Study B7981027.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the short treatment duration and the measures to minimize the risk to study participants (through the inclusion/exclusion criteria and safety monitoring), the potential risks identified in association with ritlecitinib are expected to be minimal and justified by the anticipated benefits of informing dose selection in studies evaluating ritlecitinib for the treatment of AA in children.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints
Primary:	**Primary:**
• To characterize the PK of ritlecitinib in children with AA 6 to <12 years of age.	• AUC_{24} on Day 7
Secondary:	**Secondary:**
• To further characterize the PK of ritlecitinib in children with AA 6 to <12 years of age.	• C_{max}, T_{max}, CL/F, V_Z/F and $t_{½}$ on Day 7
• To characterize the PD of ritlecitinib in children with AA 6 to <12 years of age.	• Change from baseline in interferon gamma IP-10 and lymphocyte subsets (T cell, B cell, and NK cells) on Day 7
• To evaluate the safety and tolerability of ritlecitinib in children with AA 6 to <12 years of age.	• TEAE • Treatment related AEs. • Serious AEs (SAEs) and AEs leading to discontinuation. • Clinically significant abnormalities in vital signs. • Clinically significant abnormalities in clinical laboratory values.
• To assess the overall palatability, acceptability, and tolerability of the proposed age appropriate formulation in children with AA aged 6 to <12 years of age.	• Taste assessment

4. STUDY DESIGN

4.1. Overall Design

This is an interventional, PK, PD, Phase 1, open label study in children 6 to less than 12 years of age with ≥50% scalp hair loss due to AA. The purpose of the study is to collect data to support dose selection for subsequent studies in the same population.

Participants will be screened and, if all eligibility criteria are met, will receive the first dose of IP within 28 days after the screening visit.

Participants will receive 20 mg ritlecitinib in one dose, daily, for 7 consecutive days. On Day 7 (EOT) blood samples for PK will be collected at:

- 0 hr (pre-dose)
- 0.5 hr,
- 1 hr,
- 3 hrs, and
- 8 hrs after dosing.

At least 12 evaluable participants with respect to the primary endpoint will be enrolled in the study. Participants that are not able to provide a full set of evaluable PK data or that miss more than one dose may be replaced at the discretion of the sponsor.

A follow-up visit will be conducted by phone, 28 to 35 days after the last dose of ritlecitinib.

4.2. Scientific Rationale for Study Design

The PK assessments from this study are necessary to support ritlecitinib dose selection in subsequent studies in children 6 to <12 years of age. The systemic exposure assessments from this study will provide information on whether the selected dose for children 6 to <12 years old provides exposures similar to the proposed dose for adolescents and adults. The PD endpoints of IP-10 and lymphocyte subsets will be assessed to understand if there is any difference in PD responses between children 6 to less than 12 years of age, and adults and adolescents. The open-label, 7-day study design has been reviewed by the US FDA and the EMA and agreed as part of the iPSP and PIP, respectively.

The 20 mg dose selected is predicted to provide exposures in 6 to <12 year old children, similar to the 30 mg dose in adults and adolescents.

The study is designed as a 7 day multiple dose study. Multiple doses are necessary for evaluating steady state PK because ritlecitinib has non stationary PK and steady state is achieved after >4 days of dosing.

PK samples will be collected at times of pre-dose and post-dose times of 0.5, 1, 3 and 8 hours. These sample times were selected to enable estimation of PK parameters of AUC, C_{max} and T_{max} using non-compartmental analysis methods. For calculation of AUC_{tau} at steady state, the predose concentration will be used as an estimate for the concentration of 24 hours post dose.

4.2.1. Patient Input Into Design

Surveys of children and parents were conducted to evaluate preferences and feasibility of the study, including study drug administration, blood draws, and clinic visit duration.

4.2.2. Diversity of Study Population

Reasonable attempts will be made to enroll participants with the distribution of characteristics with respect to race, ethnicity, and age to ensure the study population is representative of the patient population that will use study intervention in clinical practice.

4.2.3. Adjudication Committee

This protocol will use an independent endpoint adjudication committee to determine whether certain investigator-reported events meet the definition of disease-related safety endpoints, using predefined endpoint criteria. Further information about this endpoint adjudication committee is provided in a charter, including a description of the scope of the committee's responsibilities, the process and definitions to be utilized by the committee for adjudication, and communication plan including timelines.

The following adjudication committees are used for the B798 program:

- Opportunistic Infection Review Committee (OIRC),
- Cardiovascular Event Adjudication Committee (CVEAC),
- Malignancy Adjudication Committee (MAC), and
- Neurosafety Event Adjudication Committee (NSEAC).

Events requiring submission to an adjudication/review committee will be identified by:

- Pfizer Study Team or designee during the review of participant data listings or by
- Site monitors during routine monitoring of participant's study records

Additional types of events for review and adjudication may be identified by Pfizer.

The Pfizer Study Team or designee will notify the study site of any such events should they be identified.

The Pfizer Study Team or designee will provide a listing of specific documents needed to support event adjudication by the Adjudication/Review Committees. Obtaining and submitting the documentation will be the responsibility of the study site.

Event documentation will vary with the event requiring adjudication and may include (but not limited to): hospital discharge summaries, operative reports, clinic notes, ECGs, diagnostic tests, pathology reports, autopsy reports and death certificate information, as applicable.

Review of redacted copies of these documents by the Pfizer Study Team or designee may be performed, where ethically and scientifically justified and permitted by local regulations, to ensure completeness and quality of event documentation prior to submission to Adjudication/Review Committees.

4.2.4. E-DMC

This study will use an E-DMC. The E-DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the E-DMC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities and investigators, as appropriate.

Composition of the E-DMC and the processes under which the E-DMC operates will be documented in the E-DMC charter.

4.2.5. Choice of Contraception/Barrier Requirements

Human reproductive safety data for ritlecitinib are limited and not enough to evaluate the risk for treatment related birth defects. In animal studies (rats and rabbits) fetotoxicity and fetal malformations were observed at exposures equivalent to 49 to 55 times the MRHD. No developmental toxicity was observed at exposures equivalent to 12 to 16 times the MRHD. Although the suspicion for human teratogenicity based on the intended pharmacology of the compound is minimal, the use of a highly effective method of contraception in WOCBP is required (see Appendix 4).

The definition of WOCBP is provided in Section 10.4.3.

4.3. Justification for Dose

The selected dose for Study B7981031 is 20 mg QD. The rationale for this dose selection is as follows.

Study B7981015 was performed in adults and adolescents and evaluated 5 dosing regimens of ritlecitinib:

- 50 mg and 30 mg with and without a loading dose of 200 mg
- A 10 mg dose without loading dose.

The results from the above study indicated that the 10 mg dose did not differentiate from placebo, while the doses of 50 and 30 mg with and without loading dose demonstrated significant efficacy over placebo. The 50 mg dose (without loading dose) was identified as the regimen with optimal benefit:risk for adults and adolescents for registration.

The dose determination to support dosing in this study was based on the following considerations:

1. The systemic exposure data generated in B7981015 for adult and adolescent participants were utilized to derive the dose recommendations for children (6 to <12 years of age) using population PK modeling and simulation analysis.

2. The dose selected for children 6 to <12 years of age in Study B7981031 is expected to provide lower exposures than the 50 mg dose in the B7981015 study in adults and adolescents.

The dose of 20 mg selected for evaluation in this PK, PD study is predicted to provide exposures in children 6 to <12 years of age approximating the exposure of a 30 mg dose in adults and adolescents. The dose of 20 mg is considered to be adequate to meet the objectives of the study to characterize of PK of ritlecitinib in children.

4.4. End of Study Definition

The end of the study is defined as the date of the completion of the last scheduled procedure (as shown in the SoA) for the last participant in the trial, globally.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. If a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, race, and ethnicity. The following eligibility criteria are designed to select participants for whom participation is considered appropriate for the present study and subsequent screening in the planned long-term study. 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.

Pfizer will review eligibility criteria verified by the investigator or qualified designee to confirm that participants meet study eligibility criteria before they are enrolled into enrolled into the study. The enrollment approval process will be initiated for a participant after an informed consent document has been signed and the investigator or qualified designee has assessed the participant as eligible. The enrollment approval will be based on review of CRF/system data.

There are no enrollment minimums or maximums in any country.

5.1. Inclusion Criteria

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

Age and Sex:

1. Participants who are 6 to <12 years old at the time of the screening visit. Refer to (Section 10.4) for reproductive criteria for male and female participants.

Disease Characteristics:

2. A diagnosis of severe AA, including AT and AU, with ≥50% scalp hair loss due to AA (ie, a SALT score of ≥50) at both the Screening and Baseline visits, without evidence of terminal hair regrowth within the previous 12 months.

Other Inclusion Criteria:

3. For study participants in the EU/UK only:

   History of clinical response failure to AA treatment (such as topical, off-label pharmacologic, or hairpiece prosthetics)

   AND

   a. Participants with a history of psychological counseling for AA (as evidenced by Screening AA assessments) in the past year prior to Screening

   Participants are eligible if current psychosocial impairment is confirmed by administering all four instruments listed below and meeting the specified thresholds:

   - PROMIS® Parent Proxy Anxiety Symptoms: T-score 60-70
   - PROMIS® Parent Proxy Depressive Symptoms: T-score 60-70
   - BRIEF®2 (BRI, ERI, CRI): T-score 60-70 on any one of the 3 components of the BRIEF®2.
   - Modified CDLQI (score of ≥7)

   NOTE: For T-scores higher than 70 (PROMIS and BRIEF) see exclusion criterion 7.

   OR

   b. *Participants with no history of psychological counseling for AA in the past year prior to Screening*

   In order to be eligible for this study, participants must:

   - Have a T-score of 60-70 on any one of the 3 instruments (PROMIS®-Anxiety Symptoms or PROMIS®-Depressive Symptoms or any one of the 3 components of BRIEF®2)
   - Complete at least 5 psychological counseling sessions for AA prior to Screening
   - Be re-evaluated after completion of the psychological counseling and have a T-score of 60-70 on any one of the three instruments (PROMIS®-Anxiety Symptoms or PROMIS®-Depressive Symptoms or any one of the 3 components of BRIEF®2)

NOTE: For T-scores higher than 70 (PROMIS and BRIEF) see exclusion criterion 7.

5.2. Exclusion Criteria

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

Medical Conditions:

1. A known congenital cause of AA, other systemic diseases that may cause hair loss (eg, lupus erythematosus, thyroiditis, systemic sclerosis, lichen planus, etc) or other etiology of hair loss (eg, telogen effluvium, androgenetic alopecia, etc).

2. Conditions that may impact absorption or metabolism of IP (eg, celiac disease, cholecystectomy or gastrectomy).

3. Pre-existing hearing loss, or sudden hearing loss, or middle or inner ear disease such as chronic otitis media, cholesteatoma, Meniere's disease, labyrinthitis, or other auditory condition that is considered acute, fluctuating or progressive. If hearing loss is due to acute otitis media, participants can be rescreened at a later date, once the condition resolves.

4. Any present malignancies or history of malignancies, history of any lymphoproliferative disorder such as EBV related lymphoproliferative disorder, history of lymphoma, history of leukemia, or signs and symptoms suggestive of current lymphatic or lymphoid disease,

5. Active autoimmune disorder (other than AA), known immunodeficiency disorder, or a first degree relative with a hereditary immunodeficiency.

6. History (one or more episodes) of CMV, varicella, herpes zoster (shingles) or disseminated herpes simplex. A history of uncomplicated herpes simplex is not exclusionary.

7. Other medical or psychiatric condition (including recent [within the past year] or active suicidal ideation/behavior) that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study, including but not limited to:

    - For participants in the EU/UK with scores of >70 on the PROMIS® or any component of the BRIEF®2, or with previous history of suicidal behaviors in the past 5 years ("Yes" answer for events that occurred in the past 5 years) to any of the suicidal behavior items of the C-SSRS or with any lifetime history of serious or recurrent suicidal behavior, a risk assessment must be performed and documented by a qualified mental health professional to assess whether it is safe to participate in the trial.

    - For participants in the US and other non-EU/UK countries with a previous history of suicidal behaviors in the past 5 years ("Yes" answer for events that occurred in the past 5 years) to any of the suicidal behavior items of the C-SSRS or with any lifetime

history of serious or recurrent suicidal behavior, a risk assessment must be performed and documented by a qualified mental health professional to assess whether it is safe to participate in the trial.

- For participants in the US and other non-EU/UK countries: Clinically significant depression per the CDRS-R (T-score ≥40).

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

8. Trisomy 21 (EU/UK only)

Prior/Concomitant Therapy:

9. Current use of any prohibited concomitant medication(s) or history of discontinuation of treatment with a JAK inhibitor due to a treatment related adverse event. Refer to Section 6.9.

Prior/Concurrent Clinical Study Experience:

10. Previous administration with an investigational product (drug or vaccine) within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

Diagnostic Assessments:

11. Any laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study, including but not limited to the following:

    - Renal dysfunction defined as:

        - eCrCl normalized to BSA: Confirmed eCrCl <60 mL/min/1.73 m^2 based on Modified Schwartz equation (pediatric patients 2 to <12 years of age). See Appendix 6.

    - Hepatic dysfunction defined as:

        - Total bilirubin >1.5 × ULN (except for Gilbert's syndrome)

        - AST >1.5 × ULN

        - ALT >1.5 × ULN

    - Hematologic abnormalities defined as:

        - Absolute neutrophil count <1.2 × 10^9/L (<1200/mm^3)

- Hemoglobin <11.0 g/dL
- Platelet count <150 × 10^9/L (<150,000/mm^3)
- Absolute lymphocyte count of <0.8 × 10^9 /L (<800/mm^3)
- Any infection requiring hospitalization, parenteral antimicrobial therapy or judged to be opportunistic by the investigator within the 3 months prior to the first dose of IP or infection with HIV, hepatitis B or hepatitis C viruses according to protocol specific testing algorithms or active acute or chronic infection requiring treatment with oral antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 4 weeks prior to Day 1 or superficial skin infection within 1 week prior to Day 1, or evidence of untreated or inadequately treated active or latent mycobacterium TB infection or a positive QFT test (or equivalent) performed within 3 months prior to first dose of IP. QFT (or equivalent) test should be performed during screening if not performed within past 3 months (see Appendix 9).

NOTE: participants may be rescreened after the infection resolves.

12. Current or recent history of clinically significant severe, progressive, or uncontrolled renal (including but not limited to active renal disease or recent kidney stones), hepatic, hematological, gastrointestinal, metabolic, endocrine (particularly thyroid disease which can be associated with hair loss), pulmonary, cardiovascular, psychiatric, immunologic/rheumatologic or neurologic disease; or have any other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration, or interfere with the interpretation of study results; or in the opinion of the investigator or Pfizer (or designee), the participant is inappropriate for entry into this study, or unwilling/unable to comply with study procedures and lifestyle requirements. Significant trauma or major surgery within 1 month of the first dose of IP is also exclusionary.

Other Exclusion Criteria:

13. Not up to date with all age appropriate vaccines, including 2-dose vaccination for varicella, or vaccination with attenuated live vaccine within 6 weeks of first dose of IP.

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

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant

and their partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use an highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

5.3.2. Meals and Dietary Restrictions

There are no restrictions regarding food or drink either before or after dosing. Participants should follow their regular diet.

5.3.3. Caffeine, Alcohol, and Tobacco

Participants will abstain from ingesting caffeine or xanthine containing products (tea, coffee, cola drinks, etc) during the study (from 24 hours prior to first dose until collection of final PK sample). Use of alcohol or tobacco is not expected in this population and should not be used during the study.

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. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and any SAE.

Screen failure data are collected and remain as source and are not reported on the CRF.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if at the time of the initial screening they were disqualified for not meeting exclusion criteria 12, 10, 11 (hematological abnormalities only) or 16 and 17.

Participants not meeting inclusion criteria 12, 10, 11 may be rescreened after the exclusion interval is over as follows:

- exclusion criterion # 12 – 30 days for significant trauma,
- exclusion criterion # 10 – 30 days or 5 half-lives for investigational products

- exclusion criterion # 11 – hematological abnormalities

Participants not meeting exclusion criteria 11 may be rescreened after the exclusion interval is over and the infection resolves as follows:

- exclusion criterion # 11 – infection requiring hospitalization or parenteral treatment – 3 months after the infection resolves

- exclusion criterion # 11 – Active acute or chronic infection requiring treatment – 28 days after the infection resolves (exception for superficial skin infections – 7 days after the infection resolves)

At the rescreening visit, all screening procedures must be repeated, including lab tests and all other eligibility criteria must be met.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

For the purposes of this protocol, study intervention refers to ritlecitinib. The daily dose is 20 mg once daily and the treatment will last up to 7 days.

6.1. Study Intervention(s) Administered

The study includes a screening period of up to 28 days, a 7-day interventional period, and a 28-35 day follow-up period. The duration of study participation for each participant is approximately 9-10 weeks.

Study Intervention(s)	
Intervention Name	Ritlecitinib (PF-06651600)
Arm Name (group of participants receiving a specific treatment or no treatment)	Active study medication
Unit Dose Strength(s)	20 mg
Route of Administration	Oral
Use	Experimental
IMP or NIMP/AxMP	IMP

Study Arm(s)	
Arm Title	Active study medication
Arm Type	Active study medication
Arm Description	Participants will receive study medication, 20 mg per day, for 7 days.

Each site will receive an initial shipment with enough IP for two participants. Replacements will be provided to the study site as the initial supply is used or expired.

6.1.1. Administration

Ritlecitinib will be provided to the study sites as capsules.

For administration, the capsules will be dissolved in water and the contents of the capsule in water will be taken. No other liquids are allowed (carbonated water, soda, fruit juices). DO NOT ADD SUGAR OR ANY SWEETENER.

The first dose will be administered at the study site, in presence of the investigator or designee, who will instruct the participant and the parents/legal guardians, in detail, on how the treatment should be taken.

VERY IMPORTANT:

a. The Investigational Product must be administered immediately after preparation and never stored.

b. The capsule must be dissolved in water according to the dosing administration instructions.

c. Treatment will be administered in the morning, after breakfast.

d. Time of the administration will be documented on a daily basis. The Investigator or designee will collect this information during the study visits and record in the Case Report Form.

e. If vomiting occurs within 1 hours after administration of ritlecitinib, it must be documented and reported to the site as a missed dose. If a dose is vomited, a replacement dose should not be administered.
All episodes of vomiting will be reported as Adverse Events, regardless of how long after the administration of ritlecitinib they occurred.

6.2. Preparation, Handling, Storage, and Accountability

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

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.

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

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

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label. Site staff will instruct participants on the proper storage requirements for take home study intervention. See the Investigational Product Manual for storage conditions of the study intervention once reconstituted.

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

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record. All ritlecitinib that is taken home by the participant, both used (empty capsules) and unused capsules, must be returned to the investigator by the participant. **Returned study intervention must not be re-dispensed to the participants.**

8. Further guidance and information for the final disposition of unused study interventions are provided in the Investigational Product 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 IPM.

6.2.1. Preparation and Dispensing

A qualified staff member will dispense the study intervention in the bottles provided, in quantities appropriate according to the SoA. A second staff member will verify the dispensing. The participant's parents/legal guardians will be instructed to maintain the product in the bottle provided throughout the course of dosing and return the bottle to the site at the next study visit. The investigational product must be maintained in a locked space, out of reach of children.

The first dose of ritlecitinib will be administered at the study site, mixed with water (not carbonated).

Specific preparation and administration instructions will be provided in the IPM.

The participant's parents/legal guardians will be instructed on how to prepare and administer the next 5 doses at home, as explained in the protocol Section 6.1.1.

The last dose of IP (the 7th dose) will be administered at the study site, in the presence of the investigator or designee. The first PK sample will be drawn before administration, then at 0.5, 1, 3 and 8 hours after administration.

In the event the content of a capsule is partially spilled, all the content must be discarded and another capsule will be used. In the unlikely event that the participant will run out of IP (accidental spilling, bottle lost, etc.) the site must be contacted immediately and, if possible, replacement IP will be provided.

All used (empty) capsules must be kept and returned at the EOT visit, for drug accountability purposes.

6.3. Assignment to Study Intervention

This is an open-label study. The investigator's knowledge of the treatment assignment must not influence the decision to enroll a particular participant or affect the order in which participants are enrolled. Given the small number of participants and the nature of the study (PK, PD) it is very unlikely that the investigator decisions may be affected by bias.

6.4. Blinding

Not applicable. This is an open-label study.

6.5. Study Intervention Compliance

Ritlecitinib will be dispensed to the participants for the whole duration of the treatment (7 days). The first and last dose will be administered at the study site.

Doses 2 through 6 will be taken at home.

The investigator or designee will provide detailed instructions on how to prepare and administer the IP.

VERY IMPORTANT:

a. If vomiting occurs within 1 hours after administration of ritlecitinib, it must be documented and reported to the site.

If the preparation containing the a whole capsule is not ingested completely, the event must be documented and reported at the following visit. Do not use another capsule on the same day. Wait until the next day for the following dose.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit (phone visits on Days 2, 4 and 6, site visit on Day 7). During the phone visits, the investigator or designee will make sure the IP was administered as directed. On Day 7, compliance will be assessed by counting the returned capsules (if any). All compliance data will be recorded in the Case Report Form. Deviations from the prescribed dosage will be recorded in the Case Report Form and documented as protocol deviations.

A record of the number of ritlecitinib capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded in the CRF.

PK samples will not be collected for under-compliant participants. The site must report the reason for undercompliance (including medication errors, if appropriate). The participant will complete the safety follow-up as described in the SoA.

6.5.1. Missed doses

Between Days 2 and 5, if a dose is missed (not more than one), treatment can be continued as scheduled. The date when the dose was missed and the reason must be reported to the site.

If more than one dose is missed (consecutively or not), participants become unevaluable for PK. Once a second dose is missed, treatment must be discontinued and no additional doses of IP can be taken. The site must be notified as soon as possible. An EOT visit must be scheduled as soon as possible. During the visit, all study procedures, as outlined in the SoA, will be conducted, with the exception of the PK sample collection.

If the dose on Day 6 is missed, the participant cannot be evaluated for PK. Study treatment is considered Early Discontinued. On Day 7, no study drug is to be administered. An EOT visit will be conducted and all study procedures will be completed, with the exception of the PK sample collection.

In all cases, a safety follow-up contact will be conducted 28-35 days after the last dose of IP.

6.6. Dose Modification

Dose modification is not permitted during the study.

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

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

6.8. Treatment of Overdose

For this study, any dose of ritlecitinib greater than 20 mg per day will be considered an overdose.

There is no specific treatment for an overdose.

In the event of an overdose:

The participant or parent/caregiver should contact the site immediately and report: the dose taken, the date and time of the day and any symptoms experienced after taking the IP.

The investigator should:

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE.**

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

6.9. Prior and Concomitant Therapy

6.9.1. Prohibited Medications

Any of the following treatment regimens specified in the timeframes outlined below:

a. **At any time:** previous use of any non-B-cell selective lymphocyte-depleting agent (eg, alefacept, alemtuzumab).

b. **Within 6 months** of first dose of study intervention or 5 half-lives (if known), or until lymphocyte count returns to normal, whichever is longer: any B-cell-depleting agents, including but not limited to rituximab.

c. **Within 12 weeks** of first dose of study intervention or 5 half-lives (if known), whichever is longer:

- Any JAK inhibitor for use in any disease indication (including topical preparation)

- Immunomodulatory biologic agents.

Note: Discontinuation of any JAK inhibitor due to a treatment-related adverse event is exclusionary (see exclusion 9).

d. **Within 8 weeks** of first dose of study intervention or within 5 half-lives (if known), whichever is longer:

- Immunosuppressants (eg, cyclosporine A, azathioprine, MTX, sulfasalazine, MMF, everolimus, ibrutinib).
- Oral or injectable steroids.

e. **Within 6 weeks** of first dose of study intervention: vaccination with attenuated live vaccine.

f. **Within 4 weeks** of first dose of study intervention or 5 half-lives (if known), whichever is longer: prohibited CYP3A inducers as described in Section 6.9.2.

g. **Within 1 week** of first dose of study intervention:

- Herbal medications with either unknown properties or pharmaceutical properties that impact PK
- Prohibited CYP3A and CYP1A2 substrates as described in Section 6.9.2 (within 7 days or 5 half-lives, whichever is longer).

6.9.2. Prohibited and Permitted Concomitant CYP3A Inducers, and CYP3A and CYP1A2 Substrates

This is not an all-inclusive list. Study personnel should stay current and consult with their pharmacy to exclude all concomitant medications that are moderate to potent CYP3A inducers or sensitive or moderate sensitive CYP3A or CYP1A2 substrates. If a medication is a sensitive or moderate sensitive CYP3A or CYP1A2 substrate and is not listed below as prohibited or permitted, consultation with the Sponsor is required.

6.9.2.1. Prohibited Concomitant CYP3A Inducers and Substrates

Refer to Table 3.

6.9.2.2. Permitted Concomitant CYP3A Substrates

Sensitive CYP3A Substrates##		**Moderate Sensitive CYP3A Substrates§**
Alfentanil	Midazolam	Alprazolam
Avanafil	Naloxegol	Atorvastatin
Buspirone	Quetiapine	Colchicine
Darifenacin	Sildenafil	Rivaroxaban
Eletriptan	Simvastatin	Tadalafil
Eplerenone	Ticagrelor	
Felodipine	Triazolam	
Lovastatin	Vardenafil	
Lurasidone		

Sensitive CYP3A substrates are drugs that demonstrate an increase in AUC of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies.
Topical (including skin or mucous membranes) application of antimicrobial and antifungal medications is permitted.
§ Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥2 to <5-fold.

6.9.2.3. Prohibited Concomitant CYP1A2 Substrates

Refer to Table 4.

6.9.2.4. Permitted Concomitant CYP1A2 Substrates

Sensitive CYP1A2 Substrates	**Moderate Sensitive CYP1A2 Substrates**
Alosetron	Clozapine
Duloxetine	Theophylline
Melatonin	Olanzapine
Ramelteon	Rasagiline
Tasimelteon	Ropivacaine
Sensitive substrates are drugs that demonstrate an increase in AUC of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Topical (including skin or mucous membranes) application of antimicrobial and antifungal medications is permitted. Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥2 to <5-fold.	

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Permanent Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention may include the following: Adverse Event, Protocol Deviation, Withdrawal of Consent, Pregnancy, and/or COVID-19.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant should remain in the study to be evaluated for safety 28 to 35 days after the last dose of IP. 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.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

7.1.1. Adverse Event

Study intervention must be permanently discontinued, and the EOT Visit completed, if the participant experiences:

- 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.

All Adverse Events leading to permanent discontinuation of IP must be documented in the CRF indicating action taken with study drug as permanently discontinued. The EOT CRF page must show reason for treatment discontinuation as “Adverse Event”.

7.1.2. Protocol Deviation

Study intervention must be permanently discontinued, and the EOT Visit completed for protocol deviations such as:

- Use of prohibited medication
- Not meeting all eligibility criteria (eg, incidental monitoring findings during phone calls)
- Treatment under-compliance (missing more than one dose of IP between Day 2 and 5, missed dose on Day 6).

7.1.3. Withdrawal of Consent

Participants may withdraw from the study at any time. If the consent is withdrawn during the treatment period (Days 1 to 7), an EOT visit must be completed. If the withdrawal is complete, from all study procedures, an EOS visit study must be conducted at the same time.

7.1.4. Pregnancy

Due to the age of the participants and the short duration of treatment there is a very low probability for a pregnancy to occur during this trial.

Also, there will be no pregnancy testing between first and last dose of IP, so pregnancy cannot be detected during treatment.

7.1.5. COVID-19

If a study participant is diagnosed with COVID-19 infection during this study, study treatment will be permanently discontinued and the event will be reported as an AE or SAE, as appropriate.

An EOT visit must be conducted as soon as possible. The participant will complete the safety follow-up visit 28-35 days after the last dose of IP.

7.1.6. Temporary Discontinuation

This is a PK and PD study. Ideally, all seven doses must be taken so the PK analyses can be conducted at the end of the treatment.

Temporary discontinuations are allowed only from Day 2 and until Day 5, and only for one day. If two or more doses (consecutive or not) are missed between Day 2 and Day 5, the participant becomes unevaluable for PK and PD.

If study treatment must be interrupted for any reason, an end of treatment visit will be completed as soon as possible, followed by an End of Study visit, at 28-35 day after the last dose of IP.

7.2. Participant Discontinuation/Withdrawal From the Study

Participants may be withdrawn from the study at any time at the request of their parents/legal guardians.

If a participant decides to discontinue treatment for any reason, all efforts should be made to conduct a safety follow-up visit 28 to 35 days after the last dose of IP. If not possible (withdrawal of consent, etc.) an Early discontinuation visit will be completed. All EOT and End of Study procedures will be conducted according to the SoA. 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.

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

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study;

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and Baseline Procedures

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

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

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

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

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

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

Psychological assessments will be conducted as described in the SoA. For additional details, refer to Appendix 11 to Appendix 15.

Severity of alopecia will also be assessed at screening (SALT) and documented in the CRF.

The total blood sampling volume for individual participants in this study is approximately 20 ml for the whole study.

Study Visit	Test	Screening	EOT
Screening	Hematology	0.5 ml	0.5 ml
	Blood chemistry	0.5 ml	0.5 ml
	QFT	1 ml	
	IP-10	1 ml	1 ml
	Lymphocyte subsets	2 ml	2 ml
	Hepatitis B and C	2 ml	
	HIV	2 ml	
	Pregnancy (serum)	2 ml	
Day 7	PK		5 ml (5 × 1 ml)
Total Blood Sampling Volume		11 ml	9 ml

Additional blood tests may be required, at the Investigator's discretion.

TBV is equal to the participant's weight in kg multiplied by the estimated mL/kg (80-90 ml/kg for children). EU and WHO guidelines suggest that no more than 1% of TBV should be drawn in a 24-hour period and no more that 3% of TBV should be drawn over 4 weeks. For example, the TBV of a 6 year-old child at approximately the 5th percentile for weight, weighing 17 kg, is 1,360-1,530 mL. Per the criteria of the EU and WHO guidelines, total blood sampling volume limits for this child are 14 -15 mL of blood in 24 hours and 41-46 mL of blood in 4 weeks.

8.1.1. Baseline Procedures

All procedures listed in the SoA must be conducted at this visit.

8.1.2. Telehealth Visits

Screening, Baseline and EOT visits must be conducted at the study site.

Telehealth visits will be used to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, videoconferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring.

Study Visits at Days 2, 4 and 6, and the EOS (Follow-up) visit will be conducted by phone. Study data will be collected as described in the SoA.

The following assessments must be performed during a telehealth visit (see the SoA):

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.4.

- Review and record any new concomitant medications or changes in concomitant medications since the last contact.

- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4.

Study participants must be reminded to promptly notify site staff about any change in their health status.

8.1.3. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. The following may be performed during a home health visit (see the SoA):

- Review and record study intervention(s), including compliance and missed doses.

- Review and record any AEs and SAEs since the last contact. Refer to Section 8.4.

- Review and record any new concomitant medications or changes in concomitant medications since the last contact.

- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4.

- On day 7, the last two PK samples (3 and 8 hours post dose) may be collected at home.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

8.2. Efficacy Assessments

This is a PK, PD study. No efficacy assessments will be performed.

8.2.1. Rater Qualifications

Clinical evaluations will be completed at screening, for eligibility purposes, as follows:

- SALT score

- Taste Assessment Questionnaire

- The C-SSRS suicidal ideation and behavior risk assessment

- CDRS

- WISC-V (Wechsler Intelligence Scale for Children - 5th edition)

The Taste Assessment questionnaire is a simple assessment that can be conducted by the Study Coordinator or designee.

All other assessments require experienced personnel, with skills in interacting with children. For C-SSRS, specific documented training is required.

Additional details are provided in specific appendices and study manual, for each assessment.

For C-SSRS assessments, only qualified raters will be allowed to evaluate and/or rate participants in this study (see Appendix 11 for details).

Training material will be provided to each site, as appropriate. The level of experience with the target population (or equivalent), specific scale experience (or equivalent), and certification required (if applicable) will be listed and used to determine whether a rater is approved for a given assessment. The rater must become certified to perform selected study assessments before they can participate in the conduct of the study. For specifically defined assessments, rater training and standardization exercises may be conducted, and written documentation will be provided by the site for each rater's certification. In return, each site will be provided written documentation outlining each rater's certification for specific study assessments. Recertification may be required at periodic intervals during the study. The raters who administer specific study assessments will be documented in a centralized location and all site staff who administer ratings will be verified in the site study documentation during the conduct of the study.

To ensure consistency and reduce variability, each participant should have all assessments conducted by the same rater. Every effort will be made to have all assessments completed by the same rater.

8.3. Safety Assessments

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

8.3.1. Physical Examinations

A complete physical examination including height and weight will be performed at Screening and include, at a minimum, an assessment of the following: general appearance, skin, lymph nodes cardiovascular, respiratory, gastrointestinal and neurological and musculoskeletal systems.

Brief physical exams will be conducted at Baseline and EOT and Early Study Termination.

Severity of alopecia will also be assessed at screening as described in Appendix 10 – SALT. A minimum of 50% scalp hair loss due to AA is required to be eligible for this study.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Section 8.4.1 to Section 8.4.3.

8.3.2. Vital Signs

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Section 8.4.1 to Section 8.4.3.

8.3.2.1. Blood Pressure and Heart Rate

BP and HR measurements will be assessed in supine position with a completely automated device and using a pediatric cuff of the appropriate size. Manual techniques will be used only if an automated device is not available.

BP and HR measurements should be preceded by at least 5 minutes of rest with the participant in a supine position, in a quiet setting without distractions.

Vital signs will be taken before blood collection for laboratory tests and consist of a single measurement of HR and 3 BP measurements (3 consecutive BP readings will be recorded at intervals of at least 1 minute apart). The average of the 3 BP readings will be recorded on the CRF.

8.3.3. Clinical Safety Laboratory Assessments

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

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

All laboratory tests with values considered clinically significant and abnormal during participation in the study or within 8 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or study medical monitor.

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

See Appendix 5 for suggested actions and follow-up assessments in the event of potential DILI.

See Section 10.6.1 for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

8.3.3.1. Alternative Facilities for Clinical Safety Laboratory Assessment

Protocol-specified safety laboratory evaluations must be conducted at a Central Laboratory.

Alternatively, additional tests required for diagnosis (such as documentation of Serious Adverse Event) can be conducted at a local laboratory, in specific circumstances (time constraints, shipping unavailable, etc.) The local laboratory may be a standalone institution or within a hospital.

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/ accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

8.3.4. Pregnancy Testing

All WOCBP participating in this study must have a pregnancy test performed at Screening, Baseline and EOT visit. Definition of a WOCBP participant is provided in Section 10.4.3.

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

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

The PI will review the results of the pregnancy test as soon as they are available and communicate the results to the parents/legal guardians within the next 24 hours.

Notification of parents/legal guardians must comply with local regulations.

8.3.5. Suicidal Ideation and Behavior Risk Monitoring

Suicidal Ideation and Behavior will be assessed at Screening using the C-SSRS (Columbia Suicide Severity Rating Scale – pediatric version, baseline assessment) version for pediatric patients 6 to 11 years old (Appendix 11).

Due to the short duration of treatment, this assessment will be performed only at screening, for eligibility purposes. The assessment will not be performed at the Follow-up visit (28-35 days after the last study intervention administration).

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

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

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

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

During the active collection period as described in Section 8.4.1, each participant and parent/legal guardian will be questioned about the occurrence of AEs in a nonleading manner.

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

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

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

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

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

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

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

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

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

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.4.1, will be recorded on the AE section of the CRF.

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

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

8.4.2. Method of Detecting AEs and SAEs

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

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

8.4.3. Follow-Up of AEs and SAEs

After the initial AE or SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and

obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

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

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

8.4.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

8.4.5.1. Exposure During Pregnancy

Due to the short duration of treatment and age of participants (6 to 11 years old) EDP is unlikely to occur.

An EDP occurs if:

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

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

- If EDP occurs in a participant/participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

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

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

- Spontaneous abortion including miscarriage and missed abortion should be reported as an SAE;

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

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

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:.

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

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

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

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

8.4.5.3. Occupational Exposure

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

8.4.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.4.8. Adverse Events of Special Interest

AESIs for this study include serious or opportunistic infections, viral reactivation, decreases in lymphocytes or platelets, and dermatologic events, including urticaria and rash.

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

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

8.4.8.1. Lack of Efficacy

Not applicable.

This is a PK, PD study. The participants will receive study treatment for 7 days. No therapeutic benefit is expected.

8.4.9. 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.

Ideally, all doses should be taken after breakfast, to ensure a 24 hour interval between dosing. Taking study treatment at a later time during the day is acceptable on Days 2, 3, 4, 5. On Treatment Day 6 the dose must be taken at breakfast, to ensure a 24 hour interval before the

last dose. Missing or taking the Day 6 dose at a later time may compromise the PK results and must be reported as a protocol deviation and a medication error.

Missed doses on Days 2, 3, 4 and 5, even multiple must be reported as protocol deviation, but do not represent medication errors.

Medication errors are recorded and reported as follows:

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

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.
- Administration of expired study intervention
- Administration of study intervention that has undergone temperature excursions from the specified storage range unless it is determine by the sponsor that the study intervention under question is acceptable for use.

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.

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.

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

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

8.5. Pharmacokinetics

Blood samples to provide plasma for PK analysis will be collected into appropriately labeled tubes containing K2EDTA anticoagulant at times specified in the SoA section of the

protocol. Blood samples of approximately 1 mL, to provide approximately 0.5 mL plasma, will be collected for measurement of plasma concentrations of ritlecitinib.

When possible, an IV canula will be used, to allow collection of all 5 samples with just one venipuncture.

On Day 7, study participants who completed the treatment and are undergoing the PK sample collection may be allowed to leave the site and go home after collection of the 3rd sample (1 hour post dose) and the last two samples (3 and 8 hours post dose) can be collected at home.

If a peripheral venous catheter was installed for collection of the first 3 PK samples, it must be removed before leaving the sites. The last two samples, 3 and 8 hours post dose, will be collected by separate venipuncture.

Blood will be collected at the time points identified in the SoA section of the protocol. On the PK sampling visit (Day 7), participants will be asked about the dosing time on the day before the visits and the investigational site personnel will record it in the data collection tool (eg, CRF). Participants will be instructed to not take their daily dose at home on the PK sampling day, but to bring the dose to the investigational site for the PK sampling visit and they will be instructed at the site when to take their dose. The IP should be administered in the morning, at breakfast, to allow completion of the PK collection (8 hours) within site working hours. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. For each blood sample collection, the allowable windows are as follows for times post dose: 0.5 hr (±10 min), 1 hr (±15 min), 3 hr (±20 min) and 8 hr (±30 min). The date and exact time of dosing and the sample collection will be entered into source document and data collection tool (eg, CRF), as well as the date and time of the previous dose (one day prior to the PK sampling day). Samples obtained outside the windows specified in the SoA will be considered a protocol deviation.

- The plasma will be stored in appropriately labeled screw-capped polypropylene tubes at approximately -20°C or colder within 1 hour of collection.
- Further details regarding the collection, processing, storage and shipping of the blood samples will be provided in the lab manual.
- Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.
- The PK samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the PK processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.
- As part of understanding the pharmacokinetics of the IP, samples may be used for metabolite identification and/or evaluation of the bioanalytical method. These

data will be used for internal exploratory purposes and will not be included in the clinical report.

The shipment address and assay lab contact information will be provided to the Investigator site prior to initiation of the study. The central laboratory will provide collection materials and directions for packaging and shipment of samples and will forward samples to the contract analytical laboratory. The contract analytical laboratory will be provided with randomization codes so that only samples in the ritlecitinib treatment groups are assayed. Placebo samples may be assayed in the event of suspected error in participant randomization.

Refer to the central lab vendor manual for further information.

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

8.7. Pharmacodynamics

PD samples will be collected at screening and Day 7 only. If treatment has been early discontinued or temporarily interrupted for more than one day, PD samples will not be collected at Day 7.

The PD samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the PD processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Depending on sampling and transport constraints, it is possible that not all biomarker samples will be collected in all study regions.

All efforts will be made to obtain the PD samples at the exact nominal time relative to dosing. Please consult the laboratory manual(s) for final instructions on sample collection, storage, and shipping requirements. These manual(s) supersede the instructions listed in the applicable protocol sections. Samples that are handled according to the respective manual guidance are considered “per protocol”.

Samples will be analyzed using fit for purpose or validated analytical methods in compliance with Pfizer standard operating procedures.

As part of understanding the pharmacodynamics of the study drug and the disease under study, samples may be used for evaluation of the bioanalytical method. These data will be used for internal (ie, Pfizer) exploratory purposes and may not be included in the clinical report.

8.7.1. Biomarkers

Biomarkers are not evaluated in this study.

8.7.2. Samples for Interferon Gamma-Induced Protein 10 (IP-10) Analysis

Blood samples to provide serum for the analysis of IP-10 will be collected into appropriately labeled tubes according to the times outlined in the SoA. IP-10 samples will be collected from all participants unless the exportation of these samples from the country of origin is prohibited by local regulators or IRB/EC decision.

8.7.3. Samples for Fluorescence-Activated Cell Sorting Analysis (T Cell, B Cell, and NK Cell Subsets)

Blood samples for the assessment of percent and absolute lymphocyte subsets will be collected and will be analyzed by FACS to identify T cell, B cell, and NK cell subsets according to the times outlined in the SoA.

8.7.4. Specified Gene Expression (RNA) Research

Specified gene expression (RNA) research is not included in this study.

8.7.5. Specified Protein Research

Specified protein research is not included in this study.

8.7.6. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.7.7. Retained Research Samples for Biomarkers

Not applicable.

8.8. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.9. Health Economics

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

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in the SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Hypothesis

No statistical hypothesis will be tested in this study.

9.2. 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 treated who have at least 1 concentration.
PK Parameter	The PK parameter analysis population is defined as all participants treated who have at least 1 of the PK parameters of primary interest.
PD Parameter	The PD parameter analysis population is defined as all participants treated who have at least 1 of the PD parameters of primary interest.
Safety	All participants 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.

9.3. Statistical Analyses

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

9.3.1. Safety Analyses

Vital signs, 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.

9.3.2. Pharmacokinetic Analyses

PK parameters will be derived from the concentration time profiles using noncompartmental methods as data permit. The various PK parameters to be assessed in this study, their definition, and method of determination are outlined in Table 1. In all cases, actual PK sampling times will be used in the derivation of PK parameters.

Table 1. Definitions of PK Parameters

Parameter	Definition	Method of Determination
AUC_{24}	Area under the plasma concentration time profile over the dosing interval 24 hrs, at steady-state	Linear-log trapezoidal method
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

Table 1. Definitions of PK Parameters

Parameter	Definition	Method of Determination
$t_{½}$	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	$Dose/AUC_{24}$ after oral dose
V_Z/F	Apparent volume of distribution after oral dose	$Dose/(AUC_{24}*k_{el})$ after oral dose

- The plasma PK parameters in Table 1 will be summarized descriptively, as applicable, in accordance with Pfizer data standards. Individual participant and median profiles of the plasma concentration-time data will be plotted using actual and nominal times, respectively. Median profiles will be presented on both linear-linear and log-linear scales. Plasma concentrations will be listed and summarized descriptively by nominal PK sampling time.

9.3.3. Pharmacodynamic Analyses

All of the PD endpoints will be summarized by time point and change from baseline for these endpoints will also be summarized at specific time points as reported in the SoA.

9.3.4. Taste Assessment Analyses

Taste acceptability data will be listed and summarized descriptively (frequencies and percentages).

9.4. Interim Analyses

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

9.5. Sample Size Determination

A sample size of 12 participants was selected based on practical considerations and should provide adequate PK information.[37,38]

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent/Assent Process

The investigator or their representative will explain the nature of the study to the participant and their parent(s)/legal guardian and answer all questions regarding the study. The participant and their parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

When consent is obtained from a participant's parent(s)/legal guardian, the participant's assent (affirmative agreement) must be subsequently obtained when the participant has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a participant's decisional capacity is so limited they cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the participant's assent may be waived with source documentation of the reason assent was not obtained. If the study participant does not provide their own assent, the source documents must record why the participant did not provide assent (for example, the child is not of assenting age per local regulations or policies), how the investigator determined that the person signing the consent was the participant's parent(s)/legal guardian, the consent signer's relationship to the study participant, and that the participant's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

If study participants are minors who reach the age of majority or if a child reaches the age of assent (per local IRB/EC requirements) during the study, as recognized under local law, the child or adolescent must then provide the appropriate assent or consent to document their willingness to continue in the study. For an adolescent who reaches the age of consent, parental consent would no longer be valid. If the enrollment of emancipated minors is permitted by the IRB/EC and local law, the participant must provide documentation of legal status to give consent without the permission of a legally authorized representative.

Participants and their parent(s)/legal guardian must be informed that their participation is voluntary. The Participant's parent(s)/legal guardian 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's parent(s)/legal guardian and the study participant as applicable are 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's parent(s)/legal guardian must be informed that the participant's 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's parent(s)/legal guardian.

The participant's parent(s)/legal guardian must be informed that the participant's 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's parent(s)/legal guardian is fully informed about their right to access and correct their child's personal data and to withdraw consent for the processing of their child's personal data, keeping in mind the privacy rights that may restrict access of older adolescents' medical records by their parent(s)/legal guardian in certain regions.

The source documentation must include a statement that written informed consent and as applicable, assent, was obtained before the participant was enrolled in the study and the date the written consent/assent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Parent(s)/legal guardian and the participant must be reconsented to the most current version of the ICD(s)/assent during their participation in the study.

A copy of the ICD(s) and assent, if written, must be provided to the parent(s)/legal guardian and the participant.

A participant who is rescreened is not required to sign another ICD if the rescreening occurs within 90 days from the previous ICD signature date.

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 their actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

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

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

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will use an E-DMC. The E-DMC is independent of the study team and includes only external members. The /E-DMC charter describes the role of the E-DMC in more detail.

The E-DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the E-DMC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities and investigators, as appropriate.

10.1.6. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer sponsored- interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted.

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

EudraCT/CTIS

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

www.pfizer.com

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

Documents within marketing applications

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

Data sharing

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

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

10.1.7. Data Quality Assurance

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

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

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

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

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

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

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

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

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

10.1.8. Source Documents

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

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

Definition of what constitutes source data and its origin can be found in the Clinical Monitoring Plan, Source Document Locator, which is maintained by the sponsor.

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

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

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

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

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

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

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

- Discontinuation of further study intervention development.

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

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

10.1.10. Sponsor's Medically Qualified Individual

The contact information for the sponsor's MQI for the study is documented in the study contact list located in the supporting study documentation/study portal or other electronic system.

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

The ECC is intended to augment, not replace, the established communication pathways between the participant and their investigator and site staff, and between the investigator and sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the investigator or site staff related to the care of a participant.

10.2. Appendix 2: Clinical Laboratory Tests

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

Table 2. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	Urea and creatinine eCrCl Glucose (fasting) Sodium Potassium Chloride AST, ALT Total bilirubin Alkaline phosphatase Albumin Total protein	Local dipstick: pH Glucose (qual) Protein (qual) Albuminuria (qual) Blood (qual) Ketones Nitrites Leukocyte esterase	At screening: Serum Pregnancy test (β-hCG) IP-10 QFT HIV Hepatitis B and C At Day 1 and Day 7: Urine pregnancy test

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.

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 occunence in a patient or clinical study paiiicipant, 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 abno1mal laborato1y finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

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

• Any abno1mal laborato1y test results (hematology, clinical chemistiy, 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 abno1mal laborato1y 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 diug tl'eatment, or other therapy.
 	
• Exacerbation of a chronic or intennittent preexisting condition, including an increase in either frequency and/or intensity of the condition.
 	
• New condition detected or diagnosed after study intervention adininistration, even though it may have been present before the staii of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected diug-di·ug 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 repo1ied as an AE or SAE unless it is an intentional overdose taken with possible suicidaVself-haiming intent. Such overdoses should be repo1ied regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically significant abnonnal laborato1y findings or other abnonnal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the paiiicipant'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 paiiicipant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untowai·d medical occunence 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 sta1i of the study that do not worsen.

10.3.2. Definition of an SAE

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

a. Results in death

b. Is life-threatening

The te1m "life-threatening" in the definition of "serious" refers to an event in which the paiiicipant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

d. Results in persistent or significant disability/incapacity

- The te1m disability means a substantial dismption of a person's ability to conduct n01mal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, dianhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent eve1yday life functions but do not constitute a substantial dismption.

e. Is a congenital anomaly/birth defect

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

The event may be suspected from clinical symptoms or laborato1y findings indicating an infection in a paiiicipant exposed to a Pfizer product. The te1ms "suspected transmission" and "transmission" ai·e considered synonymous. These cases ai·e considered unexpected and handled as serious expedited cases by phaimacovigilance personnel. Such cases ai·e also considered for repo1iing as product defects, if appropriate.

g. **Other situations:**

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE repo1iing is appropriate in other situations, such as significant medical events that may jeopardize the pa1iicipant 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 dmg dependency or diug abuse.

10.3.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for repo1iing SAEs on the CT SAE Repo1i Fo1m to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

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

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs or SAEs associated with EDP or EDB Note: Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE)**
Environmental or occupational exposure to the product under study to a nonparticipant (not involving EDP or EDB)	None. Exposure to a study nonparticipant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the CT SAE Report Form.
** **EDB** is reported to Pfizer Safety using the CT SAE Report Form, which would also include details of any SAE that might be associated with the EDB.
*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form.

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE or SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the paiiicipant 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 info1mation. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE repo1ied during the study and assign it to 1 of the following categories:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual ADL.

- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADL, causing discomfo1i, but poses no significant or pennanent risk ofhann to the research paiiicipant.

- Severe: A type of AE that intenupts usual ADL, or significantly affects clinical status, or may require intensive therapeutic intervention.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occunence of each AE or SAE. The investigator will use clinical judgment to dete1mine the relationship.

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

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

- The investigator will also consult the IB and/or product infonnation, for marketed products, in their assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have provided an assessment of causality.
- There may be situations in which an SAE has occmTed and the investigator has minimal info1mation to include in the initial repo1i to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change their opinion of causality in light of followup info1mation and send an SAE followup repo1i with the updated causality assessment.
- The causality assessment is one of the criteria used when detennining regulato1y repo1iing 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 repo1iing pmposes, as defined by the sponsor. In addition, if the investigator detennines 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 Repo1i Fo1m and in accordance with the SAE repo1iing requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perfonn or aiTange 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 laborato1y tests or investigations, histopathological exaininations, or consultation with other healthcare providers.
- If a paiiicipant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmo1iem findings, including histopathology
- New or updated infonnation will be recorded in the originally submitted documents.
- The investigator will subinit any updated SAE data to the sponsor within 24 hours of receipt of the info1mation.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic DCT
• The primaiy mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT. • If the electronic system is unavailable, then the site will use the paper SAE DCT (see next section) to repo1t the event within 24 hours. • The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper fonn (as applicable) as soon as the data become available. • After the study is completed at a given site, the electronic DCT will be taken offline to prevent the entiy of new data or changes to existing data.. • If a site receives a report of a new SAE from a study paiticipant or receives updated data on a previously repo1ted SAE after the electi·onic DCT has been taken offline, then the site can repo1t this infonnation on a paper SAE fonn (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via the CT SAE Report Form
• Facsimile ti-ansmission of the CT SAE Repo1t Fo1m is the prefened method to ti·ansinit this infonnation to Pfizer Safety. • In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transpo1t Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the CT SAE Repo1t Fo1m 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 Repo1t Fo1m pages within the designated repo1ting time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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

For EU/UK only:

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 30 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

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

OR

- Must agree to use contraception/barrier as detailed below:
    - Agree to use a male condom, and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a WOCBP who is not currently pregnant.

10.4.2. Female Participant Reproductive Inclusion Criteria

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

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

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

  OR

- Is a WOCBP and agrees to use a highly effective contraceptive method (failure rate of <1% per year) with low user dependency during the intervention period and for at least 30 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.

OR

- Is a WOCBP and agrees to use a highly effective (failure rate of <1% per year) user-dependent method of contraception during the intervention period and for at least 30 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). In addition to her use of the highly effective method above, she agrees to concurrently use an effective barrier method. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for reviewing the woman's medical history, menstrual history, and recent sexual activity in order to decrease the risk of enrolling a woman with an early undetected pregnancy.

If a female participant becomes pregnant during study participation, this information will be shared with her parents/legal guardians.

Notification of parents/legal guardians must comply with local regulations.

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:.

    - Documented hysterectomy;

    - Documented bilateral salpingectomy;

    - Documented bilateral oophorectomy.

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

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

3. Postmenopausal female:

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

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

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

10.4.4. Contraception Methods

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

The following contraceptive methods are appropriate for this study:

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

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

2. Intrauterine device.

3. Intrauterine hormone releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner.

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

Highly Effective Methods That Are User Dependent

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral + barrier*
    - Intravaginal + barrier*
    - Transdermal + barrier*
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral + barrier*
    - Injectable + barrier*
8. 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.

* Acceptable barrier methods to be used concomitantly with options 6 or 7 for the study include any of the following:
    - Male or female condom, with or without spermicide (male condom and female condoms should not be used together due to risk of failure with friction);
    - Cervical cap, diaphragm, or sponge with spermicide.
    - A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-Up Assessments

Potential Cases of Drug-Induced Liver Injury

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

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to T bili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

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

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

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

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

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

Rises in AST/ALT and T bili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor..

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

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

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and T bili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

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

10.6. Appendix 6: Kidney Safety Monitoring Guidelines

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

Standard kidney safety monitoring requires assessment of baseline and postbaseline serum creatinine (Scr measurement to estimate creatinine clearance normalized to BSA [Modified Schwartz eCrCl]).

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

10.6.2. Age-Specific Kidney Function Calculation Recommendation

Modified Schwartz equation (pediatric patients 2 to <12 years of age).

- CrCl (mL/min/1.73 m^2) = (K*Ht)/Scr
- Height (Ht) in cm; serum creatinine (Scr) in mg/dl
- K (proportionally constant):
- Female child: K = 0.55
- Male child: K = 0.70

10.6.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl) will be according to

KDIGO criteria.

10.7. Appendix 7: Prohibited Concomitant Medications That May Result in DDI

This is not an all-inclusive list. This list of drugs prohibited for potential DDI concerns with the IP may be revised during the course of the study with written notification from sponsor, to include or exclude specific drugs or drug categories for various reasons (eg, emerging DDI results for the IP, availability of new information in literature on the DDI potential of other drugs).

Study personnel should stay current and consult with their pharmacy to exclude all concomitant medications that are moderate to potent CYP3A inducers or sensitive or moderate sensitive CYP3A substrates or sensitive or moderate sensitive CYP1A2 substrates. If a medication is a sensitive or moderate sensitive CYP3A substrate, or a sensitive or moderate sensitive CYP1A2 substrate, and is not listed in Table 3 and Table 4 as prohibited or permitted, consultation with the Sponsor is required.

Table 3. Prohibited Concomitant CYP3A Inducers and Substrates

Sensitive CYP3A Substrates[a]	Moderate Sensitive CYP3A Substrates[b]	Moderate to Potent CYP3A Inducers[c]
Dasatinib	Aprepitant	Avasimibe[d]
Dronedarone	Eliglustat	Bosentan
Ebastine	Pimozide	Barbiturates
Lomitapide	Rilpivirine	Carbamazepine[d]
Nisoldipine		Efavirenz
Sirolimus		Etravirine
Tacrolimus		Mitotane[d]
Tolvaptan		Modafinil
		Nafcillin
		Phenobarbital[d]
		Phenytoin[d]
		Rifabutin[d]
		Rifampin[d]
		St. John's Wort[d]
		Talviraline

a. Sensitive CYP3A substrates are drugs that demonstrate an increase in AUC of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies.
b. Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥2 to <5-fold.
c. All prohibited drugs that are CYP3A inducers require at least a 28 day or 5 half-lives (whichever is longer) washout prior to the first dose of study intervention. In a situation where appropriate medical care of a participant requires the use of a prohibited CYP3A inducer: Moderate to potent inducers of CYP3A are not permitted in the study EXCEPT in emergency situations. Note: Mitotane is not permitted for any duration due to its long half-life; however, if necessary mitotane may be used in an emergency, however the participant will then be discontinued from the study. Topical (including skin or mucous membranes) application of antimicrobial and antifungal medications is permitted.
d. Notated as potent inducers.

Table 4. Prohibited Concomitant CYP1A2 Substrates

Sensitive CYP1A2 Substrates	Moderate Sensitive CYP1A2 Substrates
Tizanidine	Pirfenidone Roflumilast
Sensitive substrates are drugs that demonstrate an increase in AUC of ≥5 fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Topical (including skin or mucous membranes) application of antimicrobial and antifungal medications is permitted. Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥2 to <5 fold.	

Investigators should consult the product label for any other medication used during the study for information regarding medication that is prohibited for concomitant use.

10.8. Appendix 8: Country-Specific Requirements

10.8.1. France

Contrat Unique

1. GCP Training

   Before enrolling any participants, the investigator and any sub-investigators will complete the Pfizer-provided Good Clinical Practice training course ("Pfizer GCP Training") or training deemed equivalent by Pfizer. Any investigators who later join the study will do the same before performing study-related duties. For studies of applicable duration, the investigator and sub-investigators will complete Pfizer GCP Training or equivalent every 3 years during the term of the study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

2. Study Intervention

   No participants or third-party payers will be charged for study intervention.

3. Urgent Safety Measures

   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.

4. Termination Rights

   Pfizer retains the right to discontinue development of ritlecitinib at any time.

10.8.2. Japan

10.8.2.1. Reporting Requirements

When becoming aware of any defect in an investigational product that meets the following conditions, the investigator must report it to the clinical trial sponsor within 24 hours (see Section 10.8.2.2). Note: Such reporting of a defect in an investigational product does not alter the AE reporting process described in Appendix 3.

- A defect that, directly or indirectly, resulted in an SAE (see Section 10.3.2) observed in a study participant, user, or other person

  OR

- A defect related to an investigational product whose recurrence might lead to death or serious deterioration in health

For reporting of complaints concerning quality of investigational products not meeting the reporting requirements above, see the detailed procedure in the "Complaints concerning investigational products" section of the IPM.

10.8.2.2. Reporting Procedure

The procedure for reporting of defects in study interventions to the sponsor should be agreed upon in advance for each study by the Safety Department and the Study Team in Development Japan and described in this section.

10.9. Appendix 9: Hepatitis B testing algorithm and full eligibility criteria

For participants in countries in which hepatitis B prevalence has been reported at a rate of >5.0%* or if required by local standard of care, participants will be tested as follows:

At screening, HBsAg and HBcAb will be tested:

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

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

c. If HBsAg is negative and HBcAb is positive, HBsAb and HBVDNA reflex testing is required:

- If HBsAb is negative, the participant must be excluded from participation in the study;
- If HBVDNA is detected, the participant must be excluded from participation in the study;
- If HBsAb is positive and HBVDNA is undetectable, the participant is eligible for study inclusion.

In all other countries, participants will be tested as follows:

At screening, HBsAg and HBcAb will be tested:

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

b. If HBsAg is positive, the participant must be excluded from participation in the

study.

c. If HBsAg is negative and HBcAb is positive, HBsAb reflex testing is required:

- If HBsAb is negative, the participant must be excluded from participation in the study;
- If HBsAb is positive, the participant is eligible for study inclusion. If the participant is included in the study, for subsequent visits no hepatitis B testing is required.

10.10. Appendix 10 – SALT

Diagnosis of AA must be performed by a qualified dermatologist (board certified or equivalent) who has experience with AA.

SALT is a quantitative assessment of alopecia severity based on scalp terminal hair loss.

Score parameters utilize a visual aid showing the division of the scalp hair into four quadrants (back, top of scalp, and both sides), with each of the four quadrants given an accurate determination of the % of scalp surface area covered, representing 24%, 40%, 18%, and 18% of the total scalp surface area, respectively.

The overall SALT score will be collected at the Screening Visit, for eligibility purposes.

The assessment will be performed by a qualified dermatologist (board certified or equivalent) who has experience with AA or a delegated member of the study staff (an experienced and qualified physician or healthcare professional).

10.11. Appendix 11 – C-SSRS

Suicidal Ideation and Behavior will be assessed at Screening using the C-SSRS (Columbia Suicide Severity Rating Scale – pediatric version, baseline assessment) version for pediatric patients 6 to 11 years old.

There are 2 versions of the C-SSRS - "C-SSRS for screening and baseline visits" and "C-SSRS for any post-baseline visits". In this study, only the baseline version will be used, for eligibility purposes.

The person conducting the assessment must be either:

a. A Mental Health Professional or

b. A study staff member with appropriate training and certification (Completion of training curriculum as required by the Columbia Lighthouse Project)

Participants who had previous history of suicidal behaviors in the past 5 years ("Yes" answer for events that occurred in the past 5 years) to any of the suicidal behavior items of the C-SSRS or any lifetime history of serious or recurrent suicidal behavior, a risk assessment must be performed and documented by a qualified mental health professional to assess whether it is safe for the participant to participate in the trial.

10.12. Appendix 12 – CDRS-R

The CDRS-R is a brief 17-item rating scale for diagnosing depression and assessing its severity. The scale is designed for use in 6- to 12-year-old children. Individuals are rated on seventeen symptom areas, including dysfunction relating to schoolwork, interpersonal relationships, psychosomatic complaints, and other thoughts and feelings commonly presenting in depressed children and adolescents. Scores are determined by a clinician through a semi-structured interview with the child and parent.[39] Interviews take about 10-15 minutes to complete and score. Each item score ranges from 1 to 5 or 1 to 7. Possible total scores ranging from 17 to 113.

10.13. Appendix 13.1 – PROMIS® Parent Proxy Short Form v2.0 – Anxiety 8a

The PROMIS Parent Proxy Short Form v2.0 – Anxiety 8a is an 8-item measure of anxiety. Each item has five response options ranging in value from 1 to 5. Raw scores are calculated by summing the values of the response to each question. The lowest possible raw score for this measure is 8 and the highest possible raw score is 40. Raw scores are transformed to T-scores using a conversion table available from the developer.[40]

T-score rescales the raw score into a standardized score with a mean of 50 and a SD of 10. Therefore, a person with a T-score of 60 is one SD above the pediatric population mean, and a T-Score of 70 is two SDs above the pediatric population mean of 50. PROMIS T-scores 70 or greater are considered severe dysfunction; T-scores from 60 to 69 are considered moderate dysfunction (PROMIS 2020a).[40]

10.13.1. Appendix 13.2 – PROMIS® Parent Proxy Short Form v2.0 – Depressive Symptoms 6a

The PROMIS Parent Proxy Short Form v2.0 – Depressive Symptoms 6a is a 6-item measure of depressive symptoms. Each item has five response options ranging in value from 1 to 5. Raw scores are calculated by summing the values of the response to each question. The lowest possible raw score for this measure is 6 and the highest possible raw score is 40. Raw scores are transformed to T-scores using a conversion table available from the developer. [40]

T-score rescales the raw score into a standardized score with a mean of 50 and a SD of 10. Therefore, a person with a T-score of 60 is one SD above the pediatric population mean, and a T-Score of 70 is two SDs above the pediatric population mean of 50. PROMIS T-scores 70 or greater are considered severe dysfunction; T-scores from 60 to 69 are considered moderate dysfunction (PROMIS 2020a). [40]

10.14. Appendix 14 - BRIEF®2

The BRIEF®2, that will be used in this study is an ObsRO parent/caregiver completed scale designed to assess executive behaviors in children and adolescents. The BRIEF®2 evaluates neuropsychological development and executive functions in adolescents. The BRIEF®2 scales assess how well the child is demonstrating behavioral or emotional control, initiating activity, engaging in planful and well-organized problem solving, and monitoring one's own social success and problem-solving outcomes.

The BRIEF®2 consists of 63 items and yields scores on nine scales, with the Inhibit and Self-Monitor scales comprising the BRI, the Shift and Emotional Control scales comprising the ERI, and the Initiate, Working Memory, Plan/Organize, Task Monitor, and Organization of Materials scales comprising the CRI. The questionnaire will be completed by the parent/caregiver of the participant.[41]

10.15. Appendix 15 - Modified CDLQI

The CDLQI is a children's version of the DLQI.[42] The CDLQI consist of 10 items that assess participant health related quality of life (daily activities, personal relationships, symptoms and feelings, leisure, work and school, and treatment). The CDLQI assesses quality of life over the last week. In this modified version, all items were modified to refer to "alopecia areata" instead of "skin" or "skin trouble".

Each item is scored from 0 to 3. Questions left unanswered are given a score of 0. Item scores are summed and expressed as usual out of a maximum score of 30.

The questionnaires are self-explanatory and can be handed to the participant who is asked to fill them in with the help of the child's parent or guardian, as necessary.

10.16. Appendix 16 - WISC-V

The WISC-V is clinical measure of cognitive ability/intelligence of children 6 to 16 years of age. Responses from the WISC-V can be used to calculate scores for intellectual functioning in several cognitive domains, as well as a composite score that represents the general intellectual ability.

The WISC-V is composed of multiple subtests and index scales, with each subtests grouped into three general categories of index scales: primary, ancillary, and complementary. Administration of the primary subtests is recommended for a comprehensive description of intellectual ability. The ancillary and complementary subtests can be administered in addition to the primary subtests to provide a broader sampling of intellectual functioning and to yield more information.

This assessment will be administered by the principal investigator or a delegated member of the study staff. Administration and Scoring Manual, Technical and Interpretive Manual will be provided to the sites.[43]

10.17. Appendix 17: Abbreviations

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

Abbreviation	Term
A1 to A3	albuminuria (KDIGO albuminuria severity standardization)
AA	alopecia areata
Abs	absolute
ADL	activity/activities of daily living
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT	alopecia totalis
AU	alopecia universalis
AUC	Area under the concentration-time curve
AUC_{tau}	area under the concentration-time curve from time zero to the end of the dosing interval
AxMP	auxiliary medicinal product
BID	twice daily
BP	blood pressure
BRI	Behavior Regulation Index
BRIEF	Behavior Rating Inventory of Executive Function
CDLQI	Children's Dermatology Life Quality Index
CDRS-R	Childhood Depression Rating Scale – Revised
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CMV	cytomegalovirus
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRI	Cognitive Regulation Index
CRO	contract research organization
CSR	Clinical Study Report
C-SSRS	Columbia – Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trial Information System
CVEAC	Cardiovascular Event Adjudication Committee
CYP	cytochrome P450
CYP1A2	cytochrome P450 family 1 subfamily A member 2
CYP3A	cytochrome P450 family 3 subfamily A
DCT	data collection tool
DDI	drug-drug interaction
DILI	drug-induced liver injury

Abbreviation	Term
EBV	Epstein Barr Virus
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment
ERI	Emotion Regulation Index
eSAE	electronic serious adverse event
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FACS	Fluorescence-Activated Cell Sorting
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
F/U	follow-up
G1 to G5	Grade (KDIGO eGFR category standardization)
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBVDNA	Hepatitis B Virus Deoxyribonucleic acid
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRQoL	health-related quality of life
HRT	hormone replacement therapy
Ht	height
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IFN	interferon
IMP	investigational medicinal product
IND	Investigational New Drug

Abbreviation	Term
INR	international normalized ratio
IP	investigational product
IP-10	induced protein 10
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
iPSP	initial pediatric study plan
IRB	Institutional Review Board
IV	intravenous(ly)
JAK	Janus kinase
K	Proportionality constant for Bedside and Modified Schwartz Equations (kidney function)
K_2EDTA	Dipotassium ethylenediaminetetraacetic acid
KDIGO	Kidney Disease: Improving Global Outcomes
LFT	liver function test
LPD	local product document
MAC	Malignancy Adjudication Committee
MMF	mycophenolate mofetil
MQI	medically qualified individual
MRHD	maximum recommended human dose
MTX	methotrexate
NA	not applicable
NIMP	noninvestigational medicinal product
NK	natural killer
NSEAC	Neurosafety Event Adjudication Committee
ObsRO	observer-reported outcomes
OIRC	Opportunistic Infection Review Committee
PD	pharmacodynamic(s)
PGI-C	Patient's global impression of change
PI	principal investigator
PIP	Pediatric Investigational Plan
PK	pharmacokinetic(s)
PR	pulse rate
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
QD	once daily
QFT	QuantiFERON test
QoL	quality of life
qual	qualitative
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SALT	Severity of Alopecia Tool
SAP	Statistical Analysis Plan

Abbreviation	Term
SC	subcutaneous(ly)
Scr	serum creatinine
SoA	schedule of activities
SOP	standard operating procedure
SRSD	Single Reference Safety Document
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	tuberculosis
T bili	total bilirubin
TBV	total blood volume
TEAE	Treatment emergent adverse event
TH1	type 1 helper T cell
TOC	table of contents
UK	United Kingdom
ULN	upper limit of normal
US	United States
UTI	urinary tract infection
WBC	white blood cell
WHO	World Health Organization
WISC-V	Wechsler Intelligence Scale for Children - 5th edition
WOCBP	woman/women of childbearing potential

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