Document Type: Final Protocol Amendment

Document Date: 08 May 2025

Study Title: A Phase 1, Investigator- and Participant-blinded, Placebo-Controlled, Randomized, Crossover Study to Assess the Relative Bioavailability of Two Formulations of AQ280 in Healthy Participants

Protocol Reference Number: ARIA-2

NCT Number: NCT07093008

Clinical Study Protocol

A Phase 1, Investigator- and Participant-blinded, Placebo-Controlled, Randomized, Crossover Study to Assess the Relative Bioavailability of Two Formulations of AQ280 in Healthy Participants

Protocol Reference:	ARIA-2 (778962)
Amendment Number:	2.0
Compound Number(s):	AQ280
Study Phase:	Phase 1

Brief Title: Comparing the Extent to Which AQ280 is Made Available in the Body After Single Oral Doses of a Capsule Formulation Versus a Tablet for Oral Suspension Formulation

Sponsor Name and Address:	Aqilion AB Redaregatan 48 SE-252 36 Helsingborg Sweden

Regulatory Agency Identifier Number(s):

IND	172968
Protocol Date:	08 May 2025

Fortrea

SPONSOR APPROVAL

PPD

08 maj 2025

PPD
Chief Medical Officer

Date

MEDICAL MONITOR NAME AND CONTACT INFORMATION

The name and contact details of the medical monitor will be provided separately.

Report SAEs within 24 hours via the contact details provided in the site documentation.

AMENDMENT DETAILS

History of Amendments

A total of 1 prior amendment has occurred, as shown in the table below.

Document	Date	Approximate Number of Participants Enrolled
Amendment 1.0	01 May 2025	0
Original Protocol	25 March 2025	0

Current Amendment

The table below provides an overview of the current amendment.

Amendment Number:	2.0
Approximate Number of Participants Enrolled:	0
Primary Reason for Amendment:	Regulatory request to amend
Other Reason for Amendment:	Not applicable
Summary of Amendment:	The time period during which contraception requirements apply to female participants has been updated.

Summary of Changes in Current Amendment

Section Number(s) and Name(s)	Description of Change	Brief Rationale for Change
Section 13.1.2 Contraception	Updated that birth control requirements for female participants will be in place until CCI after the last dose of study intervention. Additionally, female participants must refrain from donation of ova and/or participation in any activities of reproductive potential for CCI after the last dose of study intervention.	Updated to cover at least CCI CCI

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1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Primary and Secondary Objectives and Endpoints

Objective	Endpoint
Primary	
To assess the relative bioavailability of single oral doses of 100 mg AQ280 capsule formulation and 100 mg AQ280 tablet for oral suspension formulation in healthy participants	Primary PK parameters: Frel, $AUC_{0-\infty}$, $AUC_{0-tlast}$, and C_{max} Additional PK parameters: t_{max} $t_{1/2}$, CL/F, and V_z/F
Secondary	
To assess the safety and tolerability of single oral doses of 100 mg AQ280 capsule formulation and 100 mg AQ280 tablet for oral suspension formulation in healthy participants	Incidence and severity of adverse events Incidence of laboratory abnormalities, based on hematology, clinical chemistry, and urinalysis test results 12-lead electrocardiogram parameters Vital signs measurements Physical examinations

Abbreviations: $AUC_{0-\infty}$ = area under the concentration-time curve from time 0 extrapolated to infinity; $AUC_{0-tlast}$ = area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; CL/F = apparent total clearance; C_{max} = maximum observed concentration; F_{rel} = relative bioavailability; $t_{1/2}$ = apparent terminal elimination half-life; t_{max} = time of the maximum observed concentration; V_z/F = apparent volume of distribution during the terminal phase.

Overall Design

Several key aspects of this study are summarized below.

Intervention Model:	Crossover
Control:	Placebo
Active Comparator:	Not applicable
Study Intervention Assignment Method:	Randomization immediately prior to dose administration on Day 1 of Period 1
Population Type:	Healthy participants
Population Diagnosis or Condition:	Not applicable – healthy participants
Population Age:	Minimum: 18 years Maximum: 65 years
Site Distribution:	Single site

Number of Parts: 1

Blinding

The following roles will not be made aware of the treatment assignment during the study: Participants, investigators, and other members of staff involved in the study (except for designated unblinded personnel who are not directly involved in any on-study data collection [eg, PK data analysts and pharmacy, bioanalytical laboratory, biometrics, and sponsor staff]).

Number of Participants

Number randomly assigned to study intervention: 8 participants target.

Parts and Duration

Study Intervention

Total duration of study intervention for each participant: A single oral dose of AQ280 or placebo in a capsule formulation and a single oral dose of AQ280 or placebo in a tablet for oral suspension formulation.

Study Participation

Total duration of study participation for each participant: Up to approximately 7 weeks

Study participation will comprise:

- a screening period of up to 35 days
- two 3-day periods, separated by a washout period of at least 5 days between dose administrations, during which study intervention will be administered
- a follow-up period of 7 (±2) days after the final dose.

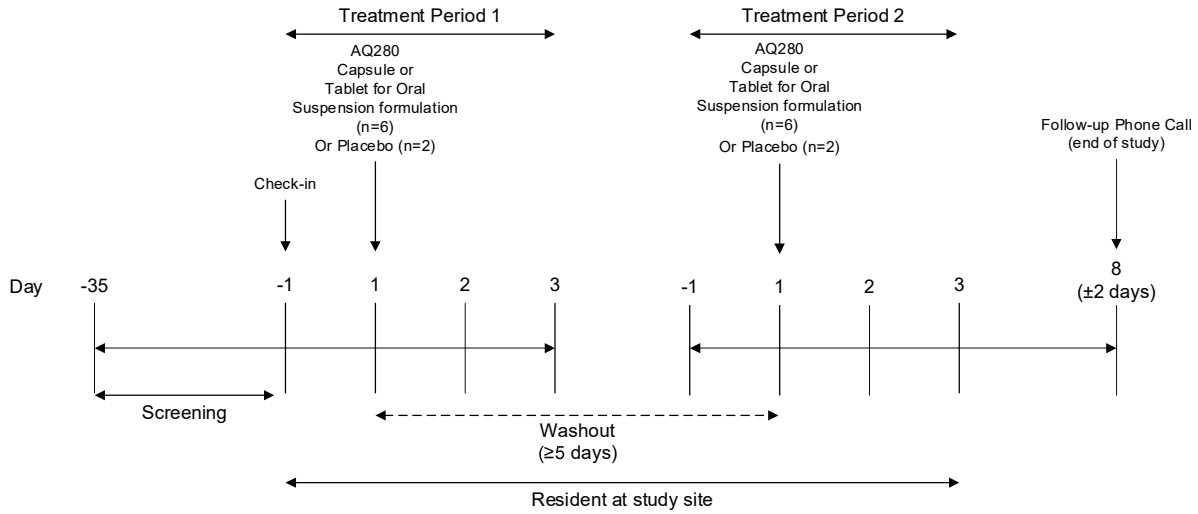
Committees

Independent Committees: Not applicable

1.2. Study Schema

The study schema is presented in Figure 1.

Figure 1: Study Schema



1.3. Schedule of Activities

A schedule of activities is presented in Table 1.

Table 1: Schedule of Activities

Study Procedures	Screening	Treatment Periods 1 and 2		Follow-up (EOS)	Early Termination	Notes
	Days -35 to -2	Day -1	Day 1 to 3	7 (±2) Days Post-Final Dose		
Informed consent	X					
Inclusion/exclusion criteria	X	X				Day -1 of Period 1 only.
Demographic data	X					
Medical history	X	X				Period 1 only. Interim medical history only on Day -1 of Period 1 only.
Urinary drugs of abuse screen	X	X				Day -1 of Period 1 only.
Alcohol test		X				Breath or urine alcohol test.
Serology	X					
Quantiferon™ TB Gold test	X					
Pregnancy test	X	X	Day 3 (Period 2)		X	Performed for all female participants in serum at screening and check-in on Day -1 and in urine at all other timepoints. A positive urine test will be confirmed with a serum pregnancy test. Day -1 of Period 1 only.
FSH	X					Performed in all female participants.
Weight	X	X				Day -1 of Period 1 only.
Height and BMI	X					
eGFR	X					Calculated using the CKD-EPI equation.
Study Residency						
Check-in		X				Day -1 of Period 1 only.

Study Procedures	Screening Days -35 to -2	Treatment Periods 1 and 2		Follow-up (EOS) 7 (±2) Days Post-Final Dose	Early Termination	Notes
		Day -1	Day 1 to 3			
Check-out			Day 3 (Period 2)			
Nonresidential visit	X					
Phone call				X		If clinically indicated during the follow-up phone call, participants may be requested to return to the study site for a follow-up visit to allow for further investigation of any new and/or ongoing adverse events.
Study Intervention Administration						
Randomization			Day 1 (Period 1)			
AQ280 capsule formulation or tablet for oral suspension formulation or placebo			Day 1 (0 h)			Dosing in Treatment Periods 1 and 2 will be separated by a washout period of at least 5 days.
Pharmacokinetics/Pharmacodynamics						
Blood sampling			Predose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours postdose		X	
CCI [redacted]			Predose, 1, 4, 8, 12, and 24 hours postdose			The 24 hours postdose timepoint will be analyzed as part of the scheduled clinical chemistry and hematology assessments.
Safety and Tolerability						

Study Procedures	Screening Days -35 to -2	Treatment Periods 1 and 2		Follow-up (EOS) 7 (±2) Days Post-Final Dose	Early Termination	Notes
		Day -1	Day 1 to 3			
Adverse event recording	X	X	Ongoing	X	X	Nonserious adverse events recorded prior to first dose administration will be documented in the participant's medical history.
Prior/concomitant medication monitoring	X	X	Ongoing	X	X	
Clinical chemistry, hematology, and coagulation	X	X	24 and 48 hours postdose		X	The Day -1 assessment may be conducted on Day-2 for Treatment Period 2.
Urinalysis	X	X	48 hours postdose		X	The Day -1 assessment may be conducted on Day-2 for Treatment Period 2.
Vital signs (blood pressure, pulse rate, oral body temperature)	X	X	Predose, 2, 4, 8, 12, 24, and 48 hours postdose		X	
12-lead ECG	X	X	Predose, 2, 8, 24, and 48 hours postdose		X	Triplicate ECG at screening, all other ECGs will be performed singly.
Continuous 12 lead ECG			X			Monitor for 12 lead ECG recording will be worn from 2 hours predose to 25 hours postdose. Extraction timepoints will be 60, 45, and 30 minutes predose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose.

Study Procedures	Screening Days -35 to -2	Treatment Periods 1 and 2		Follow-up (EOS) 7 (±2) Days Post-Final Dose	Early Termination	Notes
		Day -1	Day 1 to 3			
Physical examination	X	X	X		X	Full physical examination at screening and check-in on Day -1 of Period 1 only. A targeted physical examination will be conducted daily on Days 1 to 3 of both Treatment Periods 1 and 2 and at Early Termination,.

Abbreviations: BMI = body mass index; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = end of study; FSH = follicle-stimulating hormone.

2. INTRODUCTION

2.1. Purpose of Study

2.1.1. Background

AQ280 is a highly selective inhibitor of JAK1 that is being developed primarily for oral treatment of eosinophilic esophagitis. AQ280 blocks the signaling pathways of several cytokines including the interleukins, IL4, IL9, IL13, IL15, as well as thymic stromal lymphopoietin, which are considered key cytokines in the pathogenesis of eosinophilic esophagitis and many other immune-related diseases.

2.1.1.1. Nonclinical data

CCI

2.1.1.2. Clinical data

To the data cut-off date of 14 March 2025, AQ280 has been used in one clinical trial (ARIA-1) and a total of 66 participants have received at least 1 dose of AQ280 or placebo. Single ascending doses between 3 and 60 mg and multiple ascending doses between 9 and 60 mg QD, administered for 7 days, were evaluated.

Single oral doses of AQ280, in the range of 9 to 60 mg, administered in a fasted state, exhibited dose-proportional PK. AQ280 was rapidly absorbed following oral administration of a capsule formulations, with a median t_{max} of around CCI postdose. The apparent terminal elimination half-life ($t_{1/2}$) ranged from approximately CCI hours.

Single oral doses and multiple oral doses QD over 7 consecutive days up to 60 mg AQ280 were safe and well tolerated by healthy male and female participants. None of the participants had a severe TEAE or SAE during the study. All AQ280 treatment-related TEAEs, each of which were considered possibly related to study drug by the investigator, were mild or moderate and largely resolved without treatment. The frequency of adverse events was similar between placebo and active cohorts.

There were no treatment-related safety trends identified, and no clinically significant findings related to study drug in the vital signs, ECGs, or physical examinations during the study.

There were no obvious dose-related changes in clinical chemistry or hematology parameters. CCI [redacted].

2.1.2. Rationale for Study

The previous first-in-human clinical study used the capsule formulation. A tablet for oral suspension formulation has been developed for the upcoming Phase 2 clinical studies. This study is being conducted to compare the bioavailability of the 2 formulations for bridging purposes in the clinical development program.[1] Additionally, this study will obtain safety and tolerability data for single oral doses of 100 mg AQ280 administered to healthy participants.

Refer to Section 1.2 and Section 1.3 for more information concerning the study design.

2.2. Summary of Benefits and Risks

Healthy participants in this study will not receive any health benefit beyond an assessment of their overall health status.

The risks of participation are primarily associated with adverse reactions to study intervention. However, there may also be some minor discomfort associated with study procedures and collection of blood samples.

No important identified risks are currently defined for AQ280. Potential risks based on reported effects of other JAK inhibitors includes an increased risk of serious infection, thrombocytopenia, cancer, and cardiovascular risks. These effects are linked to long-term use of JAK inhibitors and therefore the risk to participants in this study, receiving 2 single doses of AQ280, is negligible. However, to mitigate any potential risk, participants with a history of serious infectious disease will be excluded from the study and participants will be monitored throughout the study via regular safety assessments.

The dose of study intervention to be investigated in this study is within the estimated therapeutic range or within a range that is deemed to be safe and well tolerated. This dose is not expected to pose any undue risk to the healthy participants in this study. Inclusion and exclusion criteria have been carefully considered to ensure the safety of participants and the study has been designed to enable close monitoring of participants' safety. All participants will be informed of the potential risks of study intervention(s) and procedures prior to enrollment in the study.

Considering the measures taken to minimize the risk to participants in this study, the potential risks associated with study intervention and procedures are justified by the anticipated benefits that may be afforded to patients with eosinophilic esophagitis and other immune-related diseases.

More detailed information about the known and expected benefits and risks and reasonably expected AEs may be found in the IB[2] for AQ280.

3. STUDY OBJECTIVES AND ENDPOINTS

The objectives and associated endpoints for this study are presented in Table 2.

Table 2: Objectives and Associated Endpoints

Objective	Endpoint
Primary	
To assess the relative bioavailability of single oral doses of 100 mg AQ280 capsule formulation and 100 mg AQ280 tablet for oral suspension formulation in healthy participants	Primary PK parameters: F_{rel}, $AUC_{0-\infty}$, $AUC_{0-tlast}$, and C_{max} Additional PK parameters: t_{max} $t_{1/2}$, CL/F, and V_z/F
Secondary	
To assess the safety and tolerability of single oral doses of 100 mg AQ280 capsule formulation and 100 mg AQ280 tablet for oral suspension formulation in healthy participants	Incidence and severity of adverse events Incidence of laboratory abnormalities, based on hematology, clinical chemistry, and urinalysis test results 12-lead electrocardiogram parameters Vital signs measurements Physical examinations
Exploratory	
To assess the PD response to AQ280 after single oral doses	CCI [redacted]

Abbreviations: $AUC_{0-\infty}$ = area under the concentration-time curve from time 0 extrapolated to infinity; $AUC_{0-tlast}$ = area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; CL/F = apparent total clearance; C_{max} = maximum observed concentration; F_{rel} = relative bioavailability; $t_{1/2}$ = apparent terminal elimination half-life; t_{max} = time of the maximum observed concentration; V_z/F = apparent volume of distribution during the terminal phase.

4. STUDY DESIGN

4.1. Description of Study Design

This will be a Phase 1, investigator- and participant-blinded, placebo-controlled, randomized, crossover study.

Up to 8 participants will be randomly assigned to study intervention, for an estimated total of 6 PK-evaluable participants.

Potential participants will be screened to assess their eligibility to enter the study within 35 days prior to first dose administration.

On Day 1 of Treatment Period 1, participants will be randomized to 1 of 4 intervention sequences (Table 3), such that, 2 participants will receive placebo and 6 participants will receive AQ280 and half of participants will receive the capsule formulation in Treatment

Period 1 followed by the tablet for oral suspension formulation in Treatment Period 2 whilst the other half of the participants will receive the tablet for oral suspension in Treatment Period 1 followed by the capsule formulation in Treatment Period 2.

Table 3: Intervention Sequences

Intervention Sequence	Number of Participants	Treatment Period 1	Treatment Period 2
1	1	PBO Capsule (A)	PBO Tablet for Oral Suspension (B)
2	1	PBO Tablet for Oral Suspension (B)	PBO Capsule (A)
3	3	AQ280 Capsule (A)	AQ280 Tablet for Oral Suspension (B)
4	3	AQ280 Tablet for Oral Suspension (B)	AQ280 Capsule (A)

Abbreviations: PBO = placebo

There will be a washout period of at least 5 days between dose administrations.

Participants will reside at the study site from check-in on Day -1 of Treatment Period 1 to Day 3 of Treatment Period 2 and will receive a follow-up (end of study) phone call 7 (±2) days after their final dose. Participants may be requested to return to the study site for a follow-up visit, if clinically indicated during the follow-up phone call, for the assessment of any new or ongoing adverse events which require further investigation (ie, vital signs, clinical laboratory tests, ECG, physical examination).

The total duration of study participation for each participant (from screening through end of study) is anticipated to be up to approximately 7 weeks.

Refer to Section 1.2 for the study schema and Section 1.3 for the schedule of activities.

4.2. Rationale for Study Design

A crossover design has been chosen because this gives a within-participant assessment of the effect of treatment on the PK of AQ280, whereby each participant acts as their own control, thus increasing the power of the study for the given number of participants.[1] The washout period is considered adequate to avoid significant carryover of the compound between periods.

This study will be placebo-controlled and blinded in order to minimize bias in the collection and evaluation of safety data during its conduct.

Intervention sequence will be randomized to minimize bias that may result from intervention order.

Based on the known PK of AQ280, the sample collection timing and duration of this study are considered adequate to achieve the study objectives.

4.2.1. Rationale for Comparator

Placebo has been chosen as the control intervention to assess whether any observed effects are treatment-related or simply reflect the study conditions.

Refer to Section 2.1.2.

4.3. Access to Study Intervention After End of Study

Study intervention will not be available to participants after end of study.

4.4. Start of Study and End of Study

Start of study is defined as the date the first participant signs an ICF.

End of study is defined as the date of the last participant's last assessment (scheduled or unscheduled).

Criteria and responsibilities related to early site closure or study termination are described in Section 10.5.

5. STUDY POPULATION

5.1. Selection of Study Population

Healthy participants, between 18 and 65 years of age, inclusive, will be enrolled in this study.

5.2. Rationale for Study Population

Conducting the study in healthy participants mitigates the potential confounding effects of the disease state and concomitant medications.

Male and female participants have been included as the indication is applicable to both sexes.

Individuals who do not meet criteria for study eligibility must not be enrolled via protocol waivers or exemptions.

Enrolled means a participant's agreement to participate in the study following completion of the informed consent process and screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

5.3. Inclusion Criteria

To be eligible to participate in this study, an individual must meet all the following criteria at screening, unless otherwise stated:

1. Male or female, of any race, between 18 and 65 years of age, inclusive.
    a. Females must not be pregnant or lactating.

   b. Males and females of childbearing potential must agree to use contraception, as described in Section 13.1.2.

2. Body mass index between 18.0 and 29.9 kg/m^2, inclusive.
3. In good health, as determined by no clinically significant findings from medical history, 12-lead ECG and vital signs measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [eg, suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) at screening and check-in, and from the physical examination at check-in, as assessed by the investigator or designee.
4. Able to comprehend and are willing to sign the ICF and abide by the study restrictions.

5.4. Exclusion Criteria

An individual who meets any of the following criteria at screening, unless otherwise stated, will be excluded from participation in this study:

Medical Conditions

1. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, respiratory, endocrine, or psychiatric disorder, as determined by the investigator or designee.
2. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, as determined by the investigator or designee.
3. History of stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion of orally administered drugs (uncomplicated appendectomy and hernia repair are allowed).
4. Any of the following:
   a. QTcF >450 ms in males or >470 ms in females, based on the longest value from the triplicate ECG measurements
   b. QRS duration >120 ms, based on the longest value from the triplicate ECG measurements
   c. PR interval >210 ms, based on the longest value from the triplicate ECG measurements
   d. findings which would make QTc measurements difficult or QTc data uninterpretable
   e. history of additional risk factors for torsades de pointes (eg, heart failure, hypokalemia, or family history of long QT syndrome).
5. Participants with an increased risk of thromboembolic events (eg, history of recurrent venous thrombosis or Factor V Leiden mutation).
6. Magnesium < LLN; participants with values that are borderline < LLN may be included, as determined by the investigator or designee.

7. History of any significant infectious disease, as assessed by the investigator, within 2 weeks prior to the first dose of IMP.
8. AST and/or ALT values > 1.2 × ULN.
9. Congenital nonhemolytic hyperbilirubinemia.
10. Hemoglobin value, neutrophil count (absolute), lymphocyte count (absolute), and/or platelet count < LLN; participants with values that are borderline < LLN may be included, as determined by the investigator or designee.
11. White blood cell count > ULN; participants with values that are borderline > ULN may be included, as determined by the investigator or designee.
12. eGFR < 90 mL/min/1.73 m^2 (calculated using the CKD-EPI equation[3]).
13. Significant history of herpes infection (ie, severe herpes outbreaks requiring anti-viral treatment).
14. Positive hepatitis panel and/or positive human immunodeficiency virus test. Participants whose results are compatible with prior immunization may be included.
15. Current active tuberculosis based on Quantiferon™ tuberculosis Gold test or history of latent infection.

Prior and Concomitant Therapy

16. Administration of any vaccine within 30 days prior to dosing.
17. Use or intend to use any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John's wort, within 30 days prior to dosing, considered to potentially impact participant safety or the objectives of the study, as determined by the investigator or designee.
18. Use or intend to use any prescription medications/products, other than hormone replacement therapy, oral, implantable, transdermal, injectable, intravaginal, or intrauterine contraceptives, within 14 days prior to dosing, considered to potentially impact participant safety or the objectives of the study, as determined by the investigator or designee.
19. Use or intend to use any slow-release medications/products considered to still be active within 14 days prior to dosing, considered to potentially impact participant safety or the objectives of the study, as determined by the investigator or designee.
20. Use or intend to use any nonprescription medications/products including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations within 7 days prior to dosing, considered to potentially impact participant safety or the objectives of the study, as determined by the investigator or designee.

Prior and Concurrent Clinical Study Experience

21. Participation in a clinical study involving administration of an IMP (new chemical entity) in the past 90 days or 5 half-lives of that drug (if known) prior to dosing, whichever is longer.

22. Have previously completed or withdrawn from this study or any other study investigating AQ280 and have previously received AQ280.

Diet and Lifestyle

23. Alcohol consumption of >21 units per week for males and >14 units for females. One unit of alcohol equals 12 oz (360 mL) beer, 1½ oz (45 mL) liquor, or 5 oz (150 mL) wine.
24. Positive urine drug screen at screening. Positive alcohol test result or positive urine drug screen at check-in.
25. History of alcoholism or drug/chemical abuse within 2 years prior to check-in.
26. Use of tobacco- or nicotine-containing products within 3 months prior to check-in.

Other

27. Receipt of blood products within 2 months prior to check-in.
28. Donation of blood from 3 months prior to screening, plasma from 2 weeks prior to screening, or platelets from 6 weeks prior to screening.
29. Poor peripheral venous access.
30. Participants who, in the opinion of the investigator or designee, should not participate in this study.

5.5. Lifestyle Considerations

5.5.1. Meals and Dietary Restrictions

While confined at the study site, participants will receive a standardized diet at scheduled times that do not conflict with other study-related activities.

Participants will be fasted for at least 10 hours prior to dosing until approximately 4 hours postdose, when a meal will be provided. With the exception of water given with the dose, participants will not be allowed fluids from 1 hour prior to until 1 hour after dosing. Other than the fluid restrictions on dosing days, water will be freely available at all times.

Participants will be fasted for at least 8 hours prior to collection of blood samples for clinical laboratory evaluations [redacted]

Restricted Foods and Beverages

Food and beverages containing poppy seeds are not permitted from 3 days prior to check-in until end of study.

Food and beverages containing grapefruit or Seville oranges are not permitted from 7 days prior to check-in until end of study.

5.5.2. Caffeine, Alcohol, and Tobacco

Caffeine

Caffeine-containing foods and beverages are not permitted from 48 hours prior to check-in and while at the study site.

Decaffeinated drinks are permitted while at the study site.

Alcohol

Consumption of alcohol is not permitted from 72 hours prior to check-in and throughout the study.

Tobacco

Participants will not be permitted to use tobacco- or nicotine-containing products within 3 months prior to check-in until end of study.

5.5.3. Physical Activity

Participants are required to refrain from strenuous exercise from 7 days before check-in until end of study but will otherwise maintain their normal level of physical activity during this time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

5.5.4. Other Activity

Participants are required to refrain from donation of blood from 3 months prior to screening, plasma from 2 weeks prior to screening, and platelets from 6 weeks prior to screening until 3 months after end of study.

5.6. Screen Failures

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomly assigned to study intervention. 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, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in the study (ie, screen failures) may be rescreened once at the discretion of the investigator (or designee). Rescreened participants should be assigned a new screening number for every screening/rescreening.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

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

6.1. Description of Study Intervention

Study interventions are described in Table 4.

Table 4: Study Interventions

Study Intervention	**AQ280**	**AQ280**	**Placebo**	**Placebo**
Type	Drug	Drug	Drug	Drug
Dose Formulation	Capsule	Tablet for oral suspension	Capsule	Tablet for oral suspension
Unit Dose Strength(s)	100 mg	20 mg	0 mg	0 mg
Dosage Level(s)	100 mg	100 mg	0 mg	0 mg
Dose Regimen	Single dose	Single dose	Single dose	Single dose
Route of Administration	Oral	Oral	Oral	Oral
Use	Experimental	Experimental	Placebo	Placebo
IMP/NIMP/AxMP	IMP	IMP	IMP	IMP
Sourcing	API will be provided by the sponsor (or designee), the capsules will be prepared extemporaneously by the study site pharmacy	Provided by the sponsor (or designee)	Excipients will be provided by the sponsor (or designee), the capsules will be prepared extemporaneously by the study site pharmacy	Provided by the sponsor (or designee)
Packaging and Labelling	Labelled in accordance with national laws and regulations. Packaging details will be presented in separate documentation.	Labelled in accordance with national laws and regulations. Packaging details will be presented in separate documentation.	Labelled in accordance with national laws and regulations. Packaging details will be presented in separate documentation.	Labelled in accordance with national laws and regulations. Packaging details will be presented in separate documentation.
Storage Conditions	According to instructions on label, in a location that is locked with restricted access	According to instructions on label, in a location that is locked with restricted access	According to instructions on label, in a location that is locked with restricted access	According to instructions on label, in a location that is locked with restricted access

Abbreviations: API = active pharmaceutical ingredient; IMP = investigational medicinal product.

6.2. Rationale for Study Intervention

A 100 mg dose of AQ280 has been selected for this study; to provide safety, tolerability, and pharmacokinetic data covering the dose range that may be administered in the upcoming Phase 2 study and subsequent patient studies. Additionally, the new (tablet for oral

suspension) formulation, to be used in the upcoming Phase 2 study, will be assessed alongside the capsule formulation previously administered in ARIA-1 FIH study.

Single oral doses are typically chosen for relative bioavailability studies because they are generally more sensitive than studies where steady state is attained when assessing the rate and extent of release of the drug substance from the drug product into the systemic circulation. Additionally, in the previous clinical study (ARIA-1), following multiple doses of 9, 27, and 60 mg AQ280 QD for 7 consecutive days, the PK profiles were similar on Days 1 and 7 and there was no evidence for accumulation of AQ280 in plasma; as such single dose pharmacokinetics are considered to be sufficient to characterize the PK of AQ280 for the Phase 2 study.

Single and multiple QD doses of up to 60 mg AQ280 were found to be safe and well tolerated in the previous FIH study. The exposure to AQ280 following a single dose of 60 mg AQ280 (geometric mean [CV%]: C_{max} = CCI ng/mL and $AUC_{0-\infty}$ = CCI h*ng/mL) was well below the exposure limits set for the FIH study (PK stopping criteria: C_{max} of CCI ng/mL and/or an AUC of CCI ng/mL*h). According to the population PK modelling, the predicted average unbound plasma concentration at steady state after once daily dosing of 90 mg is CCI ng/mL. This is equivalent to the concentration needed to inhibit IL-4 release by 85% in the human whole blood-based assay, compared to 70% inhibition of IL-4 release following a single dose of 60 mg AQ280. As such, a dose of 90 mg is planned for the upcoming Phase 2 study to maximize the inhibition of IL-4 release and thereby increasing the potential therapeutic effect to patients but without risking overdose or achieving complete inhibition of IL-4 release. A dose of 100 mg AQ280 has been selected for this study to cover the potential dose range for the upcoming Phase 2 study and subsequent patient studies.

In the FIH study (ARIA-1), dose escalation rules stated; for predicted pharmacologically active dose levels, dose levels should not increase such that the maximum exposure (as assessed by C_{max} and/or AUC over the time interval 0 to 24 hours postdose [AUC_{0-24}]) is predicted to increase by >3-fold for any individual participant. Exposure to AQ280 was proportional to dose for the range of 9 to 60 mg and, therefore, the PK of AQ280 is assumed to be linear. The dose escalation from 60 mg, administered in the FIH study, to 100 mg AQ280 for this study only represents a 1.7-fold increase. The target dose of 100 mg AQ280 is anticipated to be well tolerated.

Because no tolerability issues are anticipated in the fasted state, doses will be administered in the fasted state, as generally recommended for bioequivalence and relative bioavailability studies.

6.3. Dosing and Administration

Each oral dose of the capsule formulation of the study intervention will be administered with approximately 240 mL of room temperature water.

For the tablet for oral suspension formulation, the tablets will be dissolved in approximately 240 mL of room temperature water. Once all the tablets have dissolved the resulting oral suspension should be consumed by the participant within approximately 5 minutes. Following dosing, there may be visible excipients left on the dosing vessel; no rinse is required.

Participants will be dosed in numerical order while seated and will not be permitted to lie supine until 2 hours postdose, except as necessitated by the occurrence of any AEs and/or study procedures.

Meal and dietary requirements in relation to dosing are described in Section 5.5.1.

6.4. Treatment of Overdose

For this study, any dose of AQ280 greater than planned will be considered an overdose.

There is no recommended specific treatment for an overdose of AQ280.

In the event of an overdose, the investigator (or designee) should:

- contact the medical monitor immediately
- closely monitor the participant for any AE/SAE and laboratory abnormalities until AQ280 can no longer be detected systemically
- document the quantity of the excess dose as well as the duration of the overdose.

6.5. Preparation, Handling, Storage, and Accountability

6.5.1. Preparation of Study Intervention

For each batch of AQ280, the completed drug product will be released by a GMP quality engineer under GMP conditions prior to administration to participants.

Further details on the preparation of study interventions will be provided separately.

6.5.2. Handling and Storage of Study Intervention

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

All study intervention(s) must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions, with access limited to the investigator and authorized site staff.

6.5.3. Accountability of Study Intervention

The investigator, institution, or the head of the medical institution, as applicable, is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

The investigator (or designee) will maintain an accurate record of the receipt of study intervention(s).

Only participants enrolled in this study may receive study intervention(s) and only authorized staff may supply or administer study intervention(s). The investigator (or designee) will

maintain an accurate record of the disposition of study intervention(s), specifying the amount dispensed to each participant and the date of dispensing. Study intervention records will be available for inspection at any time and will be available for review by the sponsor, upon request, at the completion of the study.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of the study.

At the completion of the study, all unused AQ280 will be returned to the sponsor (or designee) or disposed of by the study site, per the sponsor's written instructions and/or in accordance with local/state/federal guidelines governing waste disposal of IMPs.

6.6. Participant Assignment, Randomization, and Blinding

6.6.1. Participant Assignment

This is a randomized study. Participants will be randomized to 1 of the study intervention sequences described in Section 4.1. Participants will be assigned a unique randomization number immediately prior to dose administration on Day 1 of Period 1.

6.6.2. Randomization

The randomization schedule will be generated prior to the study by Fortrea using a computer-generated pseudo-random permutation procedure. Each participant will be dispensed blinded study intervention, labelled with their unique randomization number, throughout the study.

6.6.3. Blinding and Unblinding

Participants, investigators, and other members of staff involved in the study except for designated unblinded personnel who are not directly involved in any on-study data collection (eg, PK data analysts and pharmacy, bioanalytical laboratory, biometrics, and sponsor staff) will remain blinded to each participant's assigned study intervention throughout the study.

In the event of a quality assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization and dispensing have been done accurately.

Sponsor safety staff may unblind the study intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to 1 or more regulatory agencies, a copy of the report, identifying the participant's study intervention assignment, may be sent to investigators in accordance with local regulations and/or the sponsor's policies.

Measures to Maintain Blinding

The following controls will be employed to maintain the blind:

- Placebo will be identical in appearance to AQ280.

- An otherwise uninvolved third party (eg, pharmacist) will be responsible for the preparation and dispensation of all blinded study intervention and will endeavor to ensure that there are no differences in the time taken to dispense following randomization.
- The participant will be instructed to avoid discussing the taste or packaging of the study intervention.

Emergency Unblinding

A sealed envelope that contains the study intervention assignment for each participant will be provided to the investigator. The sealed envelope will be retained by the investigator (or designee) in a secured area. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's study intervention assignment, unless this could delay emergency treatment of the participant. If a participant's study intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind.

6.7. Study Intervention Compliance

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

Participants will receive study intervention directly from the investigator (or designee), under medical supervision. The date and time of each dose administered at the study site will be recorded. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

Study site staff will examine each participant's hands and mouth to ensure that the study intervention was ingested.

6.8. Concomitant Therapy

Any medication or vaccine, including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements, that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use
- dates of administration, including start and end dates
- dosage information, including dose and frequency.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.8.1. Prohibited Concomitant Therapy

Participants must abstain from taking any of the therapies described in Section 5.4 during the study, unless, in the opinion of the investigator (or designee) and sponsor, the medication will not interfere with the study.

6.8.2. Permitted Concomitant Therapy

Paracetamol/acetaminophen, at doses of ≤2 grams/day for up to 3 consecutive days, hormone replacement therapy, oral, implantable, transdermal, injectable, intravaginal, and intrauterine contraceptives are permitted for use during the study. Other concomitant medication may be considered on a case-by-case basis by the investigator (or designee), in consultation with the medical monitor, if required (eg, for the treatment of an AE).

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL FROM STUDY

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to be permanently discontinued from study intervention. If study intervention is permanently discontinued, the participant may remain in the study to be evaluated at a minimum for safety. Refer to the schedule of activities for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.1.1. Criteria for Permanent Discontinuation of Study Intervention

A participant will be permanently discontinued from study intervention if any of the following criteria are met:

- change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects participant safety, as determined by the investigator (or designee)
- noncompliance with the study restrictions that might affect participant safety or study assessments/objectives, as considered applicable by the investigator (or designee)
- any clinically relevant sign or symptom that, in the opinion of the investigator (or designee), warrants participant withdrawal.
- Any of the following clinical laboratory findings:
    - evidence of clinically significant increases in liver function tests defined as 3 × ULN for AST, ALT, alkaline phosphatase, or gamma-glutamyl transferase or 2 × ULN for total bilirubin (confirmed by repeat testing).
    - clinically significant increases in serum creatinine, defined as 1.5 × ULN (confirmed by repeat testing).
    - hemoglobin decrease of >3.5 g/dL compared to levels on Day -1 of Treatment Period 1 (confirmed by repeat testing).
    - neutrophil count $<1.0 \times 10^9$/L and/or platelet count $<100 \times 10^9$/L (confirmed by repeat testing).

  - clinically significant increases in activated partial thromboplastin time or prothrombin time, defined as 2 × ULN (confirmed by repeat testing).

- QT interval corrected for heart rate using Fridericia's method (QTcF) increases >60 ms compared to baseline (predose in each Treatment Period) and/or absolute QTcF values >500 ms (confirmed with repeat testing).

If a participant is permanently discontinued from study intervention, the sponsor will be notified and the date and reason(s) for the discontinuation will be documented in the participant's eCRF.

7.2. Participant Withdrawal from the Study

A participant may withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the investigator (or designee) for safety, behavioral, or compliance reasons. This is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in the schedule of activities. Refer to the schedule of activities for data to be collected at the time of study discontinuation.

- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before withdrawal of consent.
- If a participant withdraws from the study, they may request destruction of any samples taken and not tested, and the investigator (or designee) must document this in the site study records.

Other applicable safety-related procedures may be performed at the investigator's (or designee's) and/or sponsor's discretion. If the participant is domiciled at the study site, these procedures should be performed before the participant is discharged from the study site. The investigator (or designee) may also request that the participant return for additional follow-up.

Participants who are withdrawn for reasons not related to study intervention may be replaced following discussion between the investigator and the sponsor. Replacement participants will be assigned to the same study intervention sequence as the participant they are replacing. Participants withdrawn as a result of AEs thought to be related to the study intervention will generally not be replaced.

7.3. Lost to Follow-up

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

The following actions must be taken if a participant fails to return to the study site 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 or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study are handled as part of Section 10.5.

7.4. Study Stopping Rules

The study may be discontinued at the discretion of the investigator (or designee), sponsor, or sponsor's medical monitor if any of the following criteria are met:

- AEs unknown to date (ie, not previously reported in any similar compound study with respect to their nature, severity, and/or duration)
- increased frequency, severity, and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined at check-in as baseline signs and symptoms)
- medical or ethical reasons affecting the continued performance of the study
- difficulties in the recruitment of participants
- cancelation of drug development.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the schedule of activities (Section 1.3). Additional safety assessments may be performed where clinically appropriate or if the ongoing review of the data suggests a more detailed assessment is required. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the schedule of activities, 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 (or designee) will record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Screening/Baseline Assessments and Procedures

Demographic data and medical histories will be collected from participants at screening and/or baseline. Height and weight will be measured, and body mass index will be calculated.

Blood samples will be collected for TB testing and analysis of serology, urine samples will be collected for analysis of drugs of abuse, and an alcohol test will be performed.

8.2. Efficacy Assessments and Procedures

Efficacy is not evaluated in this study.

8.3. Safety Assessments and Procedures

8.3.1. Physical Examinations

A full physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, neurological, and musculoskeletal systems and the skin.

A targeted physical examination will include, at a minimum, assessments of the heart, lungs, abdomen, and skin, as well as any other systems required to assess any reported symptoms.

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

8.3.2. Vital Signs

Oral body temperature, pulse rate, and blood pressure will be assessed.

Blood pressure and pulse measurements will be assessed whilst supine with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television or cellular phones).

Vital signs (to be taken before blood collection for laboratory tests) will be measured singly and repeated once if outside the relevant reference range.

8.3.3. Electrocardiograms

8.3.3.1. Safety 12-lead Electrocardiograms

12-lead ECGs will be obtained using an ECG machine that automatically calculates the heart rate and measures QRS duration, and RR, PR, QT, QTc, and QTcF intervals.

Assessments will be performed whilst supine and should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television or cellular phones).

At screening, 12-lead ECGs will be measured in triplicate, at approximately 1- to 2-minute intervals. Subsequent 12-lead ECGs will be measured singly and will be repeated once if outside of the reference range, unless either of the following criteria apply, upon which measurements will be repeated twice.

- QTcF >500 ms
- QTcF change from the baseline (Day 1, predose) >60 ms.

The investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

8.3.3.2. Continuous 12-lead Electrocardiograms

Continuous 12-lead ECG monitoring using a digital recorder will be performed.

All continuous 12-lead ECG data collected will be archived without extraction or analysis and will not be reported in the scope of this study.

Participants should be at rest, while supine, for at least 10 minutes (at least 5 minutes for the 0.25 hour postdose timepoint only) before the extraction timepoint and for 5 minutes from the start of each extraction timepoint (each extraction will last for 5 minutes), such that participants will be supine for a total of 15 minutes. Environmental distractions (eg, television or cellular phones) should be avoided during the resting period and during ECG recording.

Pharmacokinetic blood sampling should always be performed after the ECG extraction time window.

8.3.4. Clinical Laboratory Evaluations

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- All protocol-required laboratory tests, as defined in Section 13.2, must be conducted in accordance with the laboratory manual.
- If laboratory values from non-protocol specified laboratory tests performed at the study site's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE), then the results must be recorded.

8.4. Adverse Events and Serious Adverse Events

8.4.1. Definitions of Adverse Events and Serious Adverse Events

Definition of an Adverse Event
An AE is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Additional details and clarifications for AEs are presented in Section 12.1.
Definition of a Serious Adverse Event An SAE is defined as any untoward medical occurrence that at any dose either:
Results in Death
Is Life Threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires Inpatient Hospitalization or Prolongation of Existing Hospitalization In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in Persistent or Significant Disability/Incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a Congenital Anomaly/Birth Defect
Other Situation Medical or scientific judgment should be exercised by the investigator in deciding whether expedited SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent 1 of the other

outcomes listed in the above definition. These events should usually also be considered serious.

Examples of such events include intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions that do not result in hospitalization or development of intervention dependency or drug abuse.

8.4.2. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All SAEs will be collected from the signing of the ICF until 30 days after the last dose of study intervention.

All AEs will be collected from the start of study intervention until end of study.

8.4.3. Identifying Adverse Events and Serious Adverse Events

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.

8.4.4. Recording of Adverse Events and Serious Adverse Events

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The investigator (or designee) will record all relevant AE/SAE information.

It is not acceptable for the investigator to send photocopies of the participant's medical records in lieu of completion of the SAE form. There may be instances when copies of medical records for certain cases are requested by sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Further details on assessing severity and causality of AEs and SAEs are in Section 12.3 and Section 12.4.

8.4.5. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contact. All AEs/SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (Section 7.3).

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor to

elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded in the originally submitted documents.

8.4.6. Reporting of Serious Adverse Events

All SAEs will be recorded and reported to the sponsor (or designee) immediately and under no circumstance should this exceed 24 hours. The investigator (or designee) will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs after conclusion of study participation or SAEs after 30 days following the last dose of study intervention. However, if the investigator learns of any SAE, including a death, at any time after 30 days following the last dose of study intervention, and they consider the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

Reporting of Serious Adverse Events Using the Paper Data Collection Tool

Email or facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information.

8.4.7. Regulatory Reporting Requirements for Serious Adverse Events

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

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

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB or package insert, as applicable, and will notify the IRB/EC, if appropriate, according to local requirements.

8.4.8. Serious and Unexpected Adverse Reaction Reporting

SUSARs are a subset of SAEs and must be reported to the appropriate regulatory authorities in accordance with local regulations and/or the sponsor’s policies.

8.4.9. Disease-related Events or Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

Not applicable.

8.5. Pregnancy and Postpartum Information

8.5.1. Participants Who Become Pregnant During the Study

Pregnancies in female participants, who become pregnant after the first dose of study intervention and up to 5 half-lives following the last dose of study intervention, will be followed for 1 year post-delivery or until the discontinuation of the pregnancy for the determination of outcome (including congenital abnormalities and/or developmental outcomes).

If a pregnancy is reported, the investigator (or designee) will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the pregnancy.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, or ectopic pregnancy) are considered SAEs and will be reported as such.

The participant will be followed to determine the outcome of the pregnancy. The investigator (or designee) will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator (or designee) will be reported to the sponsor as described in Section 8.4.6. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

8.5.2. Participants Whose Partners Become Pregnant

Pregnancies in female partners of male participants, who become pregnant after the first dose of study intervention and up to 5 half-lives following the last dose of study intervention, will be followed for 1 year post-delivery or until the discontinuation of the pregnancy for the determination of outcome (including congenital abnormalities and/or developmental outcomes).

If a pregnancy is reported, the investigator (or designee) will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the pregnancy after obtaining the necessary signed ICF from the female partner.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, or ectopic pregnancy) are considered SAEs and will be reported as such.

The female partner will be followed to determine the outcome of the pregnancy. The investigator (or designee) will collect follow-up information on the female partner and the neonate, and the information will be forwarded to the sponsor.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator (or designee) will be reported to the sponsor as described in Section 8.4.6. While the investigator is not obligated to actively seek this information, he or she may learn of an SAE through spontaneous reporting.

8.6. Medical Device Product Complaints for Drug/Device Combination Products

Not applicable.

8.7. Pharmacokinetics

Blood samples will be collected for measurement of plasma concentrations of AQ280.

Instructions for the collection and handling of biological samples will be provided separately. The actual date and time (24-hour clock time) of each sample collection will be recorded.

Samples will be used to evaluate the PK of AQ280. Samples collected for analyses of AQ280 may also be used for exploratory analysis of metabolites, or to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Plasma concentrations of AQ280 will be determined using validated analytical procedures. Specifics of these analytical methods will be provided separately.

8.8. Genetics

Genetics are not evaluated in this study.

8.9. Biomarkers

8.9.1. Pharmacodynamics

Blood samples will be collected for CCI [redacted].

Instructions for the collection and handling of biological samples will be provided separately. The actual date and time (24-hour clock time) of each sample collection will be recorded.

Samples will be used to evaluate the PD of AQ280. Samples collected for analyses may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

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

8.10. Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

8.11. Medical Resource Utilization

Medical resource utilization and health economics are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

The final analysis will be conducted on all participant data in the relevant analysis set at study completion.

The SAP will be finalized prior to unblinding (interim or final) and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1. Analysis Sets

The analysis sets are described in Table 5.

Table 5: Analysis Sets

Set	Description
All Participants	All participants who signed the informed consent form and had any study assessments recorded in the database, as per protocol.
Safety	All participants who received at least 1 dose of study intervention (AQ280 or placebo). Participants will be analyzed according to the study intervention they actually received.
Pharmacokinetic	All participants who received at least 1 dose of study intervention (AQ280) and have at least 1 valid pharmacokinetic concentration.

9.2. Analyses Supporting the Primary Objective

Pharmacokinetic parameters will be determined from plasma concentrations of AQ280 using standard noncompartmental methods. Full details of PK parameters and the PK analysis will be presented in the SAP for this study.

Plasma concentrations of AQ280 and PK parameters will be listed and summarized. Individual and mean AQ280 plasma concentration-time profiles will also be presented graphically.

The natural log-transformed primary PK parameters (C_{max}, $AUC_{0-\infty}$, and $AUC_{0-tlast}$) will be analyzed using a mixed model. Estimates of geometric mean least squares mean ratios, together with their corresponding 90% confidence intervals, will be derived for the comparisons of the PK parameters:

AQ280 Tablet for Oral Suspension (test) versus AQ280 Capsule (reference)

9.3. Analysis Supporting the Secondary Objective

Vital signs and ECG data will be listed and may be presented graphically if deemed appropriate. Adverse events will be coded using the MedDRA and will be listed and summarized using descriptive statistics. All other safety data will be listed only. No formal statistical analysis of safety data are planned.

9.4. Analysis Supporting the Exploratory Objective

Pharmacodynamic parameters and change from baseline will be listed and summarized. No formal statistical analysis of PD data is planned.

9.5. Safety Analyses

Safety analyses are presented in Section 9.3.

9.6. Other Analyses

Not applicable.

9.7. Interim Analyses

No formal interim analyses are planned.

9.8. Sample Size Determination

A total of 8 participants will be randomly assigned to study intervention, such that 6 PK evaluable participants will complete the study.

No formal statistical assessment of sample size has been conducted. However, the number of participants is common in early clinical pharmacology studies and is considered sufficient to achieve the objectives of the study.

9.9. Protocol Deviations

Plans for detecting, reviewing, and reporting any deviations from the protocol will be described in separate documentation.

10. GENERAL CONSIDERATIONS: REGULATORY, ETHICAL, AND STUDY OVERSIGHT

10.1. 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
- ICH GCP guidelines
- Applicable laws and regulations.

Investigator Responsibilities

The protocol, ICF, IB, and other relevant documents must be 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 and regulatory authority (as locally required) approval before implementation of changes to the study design, except for changes necessary to eliminate an immediate hazard to participants.

The investigator will be responsible for the following:

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

10.2. Committees

Not applicable.

10.3. Informed Consent Process

The investigator (or designee) will explain the nature of the study to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

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

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

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

Rescreening

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

Handling of screen failures, including conditions and criteria for which rescreening is acceptable, is presented in Section 5.6.

Use of Remaining Samples for Optional Exploratory Research

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator (or designee) will explain to each participant the objectives of the exploratory research, if applicable.

10.4. Data Protection

Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that their study-related data may be examined by sponsor auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The contract between the sponsor and study sites will specify responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.

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

10.5. Early Site Closure or Study Termination

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

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

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

For study termination:

- discontinuation of further study intervention development.

For site termination:

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

- inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- total number of participants included earlier than expected.

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

11. GENERAL CONSIDERATIONS: RISK MANAGEMENT AND QUALITY ASSURANCE

11.1. Quality Tolerance Limits

Quality tolerance limits will be pre-defined, in separate documentation, to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

11.2. Data Quality Assurance

All participant data relating to the study will be recorded on an eCRF 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 electronically signing the eCRF. Guidance on completion of eCRFs will be provided separately.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

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

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

The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator or designee in accordance with 21 CFR 312.62(c). 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.

11.3. Source Data

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

Data reported on the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator (or designee) may need to request previous medical records or transfer records, depending on the study.

Definition of what constitutes source data can be found in separate documentation.

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

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

12. APPENDIX: ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS – DEFINITIONS, SEVERITY, AND CAUSALITY

12.1. Further Details and Clarifications on the Adverse Event Definition

Events Meeting the Definition of an Adverse Event
Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator or designee (ie, not related to progression of underlying disease).
Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.
Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. 'Lack of efficacy' or 'failure of expected pharmacological action' also constitutes an AE or SAE.

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

12.2. Further Details and Clarifications on the Serious Adverse Event Definition

Not applicable.

12.3. Severity

The investigator (or designee) will assess the intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

Mild
An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities.
Moderate
An event that causes sufficient discomfort to interfere with normal everyday activities.
Severe
An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

12.4. Causality

The investigator (or designee) will determine the relationship of the AE to the study intervention using the guidelines below.

Not Related
The AE is definitely caused by the participant's clinical state or the study procedure/conditions.
Unlikely Related
The temporal association between the AE and the study intervention is such that the study intervention is not likely to have any reasonable association with the AE.
Possibly Related
The AE follows a reasonable temporal sequence from the time of study intervention administration but could have been produced by the participant's clinical state or the study procedures/conditions.
Related
The AE follows a reasonable temporal sequence from administration of the study intervention, abates upon discontinuation of the study intervention, follows a known or hypothesized cause effect relationship, and (if appropriate) reappears when the study intervention is reintroduced.

13. APPENDIX: DEFINITIONS AND SUPPORTING OPERATIONAL DETAILS

13.1. Contraception and Pregnancy Testing

13.1.1. Definitions Related to Childbearing Potential

Female of Childbearing Potential
Premenopausal female who is anatomically and physiologically capable of becoming pregnant following menarche.
Female of Nonchildbearing Potential
Surgically Sterile Female who is permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred ≥6 weeks, or at the investigator's discretion, prior to screening. **Postmenopausal** Female ≥45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory FSH level of ≥40 mIU/mL, if applicable. In the absence of 12 months of amenorrhea, a single FSH measurement to be taken at the time of screening is insufficient to diagnose postmenopausal status; therefore, these participants will be considered to be of childbearing potential and will be required to use contraception as described. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease, or polycystic ovarian disease; or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea (eg, oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, selective estrogen receptor modulators, or chemotherapy).

Females on hormone replacement therapy with FSH levels <40 mIU/mL may be included at the discretion of the investigator. Women aged ≥60 years old whose FSH values are not ≥ 40 mIU/mL may be included at the discretion of the investigator and in consultation with the sponsor.
Fertile Male
A male that is considered fertile after puberty.
Infertile Male
Permanently sterile male via bilateral orchiectomy.

13.1.2. Contraception

Female Participants

For female participants of childbearing potential, 2 methods (1 primary highly effective [low user dependency] and 1 secondary) of birth control are required from the time of signing the ICF until CCI after the last dose of study intervention.
Primary acceptable highly effective methods of contraception with low user dependency include:
• surgical method performed at least 3 months prior to screening:
  ○ bilateral tubal ligation
  ○ Essure® (hysteroscopic bilateral tubal occlusion) with verbal confirmation of occlusion of the fallopian tubes
• hormonal implant (as prescribed)
• hormonal or non-hormonal intrauterine device
• vasectomized male partner (sterilization performed at least 90 days prior to screening, with verbal confirmation of surgical success, and the sole partner for the female participant).
A secondary (barrier) method of contraception includes:
• condom with spermicide.
Female participants who are of nonchildbearing potential will not be required to use contraception.
All female participants should refrain from donation of ova and/or participation in any activities of reproductive potential (eg, in vitro fertilization) from check-in until CCI after the last dose of study intervention.

Male Participants
Male participants with partners of childbearing potential are required to use the following contraceptive method: • condom and spermicide (even if the participant has a history of vasectomy). Additionally, a second method of acceptable contraception is required from check-in until 90 days after end of study.

Acceptable methods of contraception for female partners include:

- hormonal injection
- combined oral contraceptive pill or progestin/progestogen-only pill
- combined hormonal patch
- combined hormonal vaginal ring
- surgical method (bilateral tubal ligation or Essure® [hysteroscopic bilateral tubal occlusion])
- hormonal implant
- hormonal or non-hormonal intrauterine device

An acceptable method of contraception for the male participant is:

- vasectomy that has been performed at least 90 days prior to screening, with verbal confirmation of surgical success.

For male participants (even with a history of vasectomy), sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from the time of the first dose until 90 days after end of study.

Male participants are required to refrain from donation of sperm from check-in until 90 days after end of study.

Sexual Abstinence and Same-sex Relationships

Participants who practice true abstinence because of the participant's lifestyle choice (ie, the participant should not become abstinent just for the purpose of study participation) are exempt from contraceptive requirements. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. If a participant who is abstinent at the time of signing the ICF becomes sexually active, they must agree to the contraceptive requirements, and ensure their partners agree to the contraceptive requirements, as previously described.

For participants who are exclusively in same-sex relationships, contraceptive requirements do not apply. If a participant who is in a same-sex relationship at the time of signing the ICF becomes engaged in a heterosexual relationship, they must agree to the contraceptive requirements, and ensure their partners agree to the contraceptive requirements, as previously described.

13.1.3. Pregnancy Testing

Follicle-stimulating hormone and pregnancy tests will be performed in all female participants.

13.2. Clinical Laboratory Evaluations

The clinical laboratory evaluations shown below will be performed by a local laboratory. Additional analyses may be performed at any time during the study, as determined necessary by the investigator or study site, or as required by local regulations.

Chemistry	Hematology	Urinalysis
Alanine aminotransferase	Hematocrit	Bilirubin
Albumin	Hemoglobin	Blood
Alkaline phosphatase	Mean cell hemoglobin	Color and appearance
Aspartate aminotransferase	Mean cell hemoglobin concentration	Glucose
Bicarbonate	Mean cell volume	Ketones
Blood urea nitrogen	Platelet count	Leukocyte esterase
Calcium	Red blood cell (RBC) count	Nitrite
Chloride	RBC distribution width	Microscopic examination (if protein, leukocyte esterase, nitrite, or blood is positive)
Cholesterol	White blood cell (WBC) count	pH
Creatinine	WBC differential (absolute and percentage):	Protein
Gamma-glutamyl transferase	Basophils	Specific gravity
Glucose	Eosinophils	Urobilinogen
Magnesium	Lymphocytes	
Phosphorus	Monocytes	
Potassium	Neutrophils	
Sodium		
Total bilirubin[a]		
Total protein		
Uric acid		
Serology[b]	**Coagulation**	**Hormone panel (females only)[b]**
Hepatitis B surface antigen	Activated partial thromboplastin time	Follicle-stimulating hormone
Hepatitis C antibody	International normalized ratio	Serum pregnancy test (human chorionic gonadotropin)[c]
Human immunodeficiency virus (HIV-1 and HIV-2) antibodies and p24 antigen	Prothrombin time	Urine pregnancy test[c]
Other[b]		
Tuberculosis (QF Gold test)		

a Direct and indirect bilirubin will be analyzed if total bilirubin is elevated.
b Performed at selected timepoints only. Refer to schedule of activities (Section 1.3).
c A positive urine pregnancy test will be confirmed with a serum pregnancy test.

13.3. Country/Region-Specific Differences

Not applicable.

13.4. Prior Protocol Amendments

The protocol amendment summary of changes for the current amendment is located before the table of contents. Details of prior amendments are presented below, commencing with the most recent.

Amendment 1.0: 01 May 2025

Section Number(s) and Name(s)	Description of Change	Brief Rationale for Change
1.3 Schedule of Activities (Table 1) and Section 4.1 Description of the Study Design	Added that, if clinically indicated during the follow-up phone call, participants may be requested to return to the study site for a follow-up visit to allow for further investigation of new and/or ongoing adverse events.	To ensure in-person investigations (ie, vital signs, clinical laboratory tests, ECG, physical examinations) can be conducted if clinically indicated during the follow-up period.
Section 1.3 Schedule of Activities (Table 1)	Added that a full physical examination should be conducted at screening and a daily targeted physical examination should be conducted on Days 1 to 3 of Treatment Periods 1 and 2.	To ensure that any physical abnormalities are captured.
Section 1.3 Schedule of Activities (Table 1)	Updated that the pregnancy test at check-in on Day -1 must be a serum pregnancy test rather than a urine pregnancy test confirmed by a serum test.	The serum pregnancy test has greater accuracy.
Section 5.3 Inclusion Criteria	Inclusion criterion #2 updated to amend the BMI upper limit to 29.9 kg/m^2.	Obese participants should not be included due to the possibility of underlying health issues.
Section 5.4 Exclusion Criteria	Exclusion criterion #4 updated that the QTcF, QRS duration, and PR interval will be assessed based on the longest value obtained from the triplicate ECG measurements rather than the mean value.	To ensure that any transient or intermittent ECG abnormalities will be fully captured.
Section 7.1.1 Criteria for Permanent Discontinuation of Study Intervention	Criteria for clinical laboratory findings and changes in QTcF have been added which would lead to the discontinuation of a participant from the study intervention.	Clarify clinically significant laboratory findings or changes in QTcF that would necessitate participant withdrawal from the study intervention.

Section Number(s) and Name(s)	Description of Change	Brief Rationale for Change
Section 8.3.1 Physical Examinations	Updated the description of a full physical examination to also include the musculoskeletal system and the skin. Added the description of a targeted physical examination. Removed the description of a symptom-directed physical examination.	Alignment with changes to the Schedule of Activities which removed symptom-directed physical examination and added daily targeted physical examinations in the treatment periods.
Section 8.5.1 Participants Who Become Pregnant During the Study and Section 8.5.2 Participants Whose Partners Become Pregnant	The period for which pregnancy in female participants or the female partners of male participants will be followed has been extended from 90 days after the end of the study until 1 year post-delivery or until the discontinuation of the pregnancy.	To ensure the outcomes of any pregnancy are captured fully.
Section 13.1.2 Contraception	Updated that female participants of childbearing potential are required to use, as a primary method of birth control, a highly effective method of contraception with low user dependency and the list of primary acceptable methods of contraception has been updated accordingly.	Teratogenic effects were observed in nonclinical embryo-fetal studies of AQ280 in mice.
Section 13.1.2 Contraception	Updated that birth control requirements for female participants will be in place until CCI after the end of the study. Additionally, female participants must refrain from donation of ova and/or participation in any activities of reproductive potential for CCI after the end of the study.	Updated to CCI this is in alignment with contraception guidelines CCI

14. APPENDIX: GLOSSARY OF TERMS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
$AUC_{0-\infty}$	area under the concentration time curve from time 0 extrapolated to infinity
$AUC_{0-tlast}$	area under the concentration time curve from time 0 to the time of the last quantifiable concentration
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	good clinical practice
GMP	good manufacturing practice
HIPAA	Health Insurance Portability and Accountability Act
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IL	interleukin
IMP	investigational medicinal product
IND	investigational new drug
IRB	institutional review board
JAK	Janus kinase
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no observed adverse effect level
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
QTL	quality tolerance limit
SAE	serious adverse event

SAP	statistical analysis plan
TB	tuberculosis
TEAE	treatment-emergent adverse event
t_{max}	time of the maximum observed concentration
TMF	trial master file
ULN	upper limit of normal
US	United States
WHO	World Health Organization

15. APPENDIX: REFERENCES

1. Food and Drug Administration. Guidance for Industry: Bioavailability Studies Submitted in NDAs or INDs - General Considerations. Food and Drug Administration; 2022.

2. Aqilion. AQ280 - Investigator's Brochure (Edition 2.0). TBC.

3. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race. N Engl J Med. 2021 Nov 4;385(19):1737–49.