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A Randomized, Double-blind, Placebo-controlled, Single and Multiple Ascending Dose, and Food Effect Evaluation Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of AQ280 in Healthy Subjects

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Protocol Reference: ARIA-1
Labcorp Drug Development Study: 8493409

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Minor changes:

1. The Springfield House address has been removed from the cover page and Study Identification page because the Labcorp Clinical Research Unit Ltd. in the United Kingdom is moving to a new building and some dose groups in the study will be done at the new site.
2. The amendment/version number and date were updated throughout the protocol.

Protocol

A Randomized, Double-blind, Placebo-controlled, Single and Multiple Ascending Dose, and Food Effect Evaluation Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of AQ280 in Healthy Subjects

Protocol Status: Final
Protocol Version: 5
Protocol Date: 30 January 2023

Investigational Medicinal Product: AQ280

Protocol Reference: ARIA-1
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PPD

SPONSOR APPROVAL

I have read the protocol and approve it:

PPD

INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

PPD

STUDY IDENTIFICATION

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SYNOPSIS

Study Title

A Randomized, Double-blind, Placebo-controlled, Single and Multiple Ascending Dose, and Food Effect Evaluation Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of AQ280 in Healthy Subjects

Objectives and Endpoints

Objectives	Endpoints
Primary:	
• to evaluate the safety and tolerability of single and multiple ascending oral doses of AQ280, and to determine a safe therapeutic range of AQ280 in healthy subjects	• number of TEAEs per subject • clinically significant abnormalities in vital signs (systolic and diastolic blood pressure, pulse rate, and oral body temperature) • abnormal ECG (QTcF interval of >450 msec for males and >470 msec for females, or change from baseline of >30 msec) measured from Day 1 (postdose) up until 48 hours postdose in Part A and up to the follow-up visit in Part B • clinically significant changes in laboratory evaluations
Secondary:	
• to determine the PK of AQ280 after single and multiple oral doses • to determine the PK of the AQ280 main metabolite, AQ282, after single and multiple oral doses • to determine the effect of food on the PK of AQ280 after single oral dose	Part A (SAD): • primary PK parameters derived from plasma concentration-time profile of AQ280: $AUC_{0-\infty}$, C_{max} ($AUC_{0-tlast}$ may be included as a primary PK parameter if $AUC_{0-\infty}$ cannot be calculated) • primary PK parameters derived from plasma concentration-time profile of the AQ280 main metabolite, AQ282: $AUC_{0-\infty}$, C_{max} ($AUC_{0-tlast}$ may be included as a primary PK parameter if $AUC_{0-\infty}$ cannot be calculated) • comparison of the primary PK parameters of AQ280 after single dose administration in the fasted state and in the fed state Part B (MAD): • primary PK parameters derived from plasma concentration-time profile of AQ280 on Day 1 and Day 7: AR, AUC_{τ}, C_{max} • primary PK parameters derived from plasma concentration-time profile of the AQ280 main metabolite, AQ282, on Day 1 and Day 7: AUC_{τ}, C_{max}
Exploratory:	
[redacted]	CCI [redacted]

Objectives	Endpoints
Exploratory (continued):	
• CCI [redacted]	CCI [redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviations: AR = accumulation ratio; $AUC_{0-\infty}$ = 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; AUC_{τ} = area under the concentration-time curve over a dosing interval; CL/F = apparent total clearance; C_{max} = maximum observed concentration; CCI [redacted]
ECG = electrocardiogram; CCI [redacted] MAD = multiple ascending dose;
PD = pharmacodynamic; PK = pharmacokinetic(s); QTcF = QT interval corrected for heart rate using Fridericia's method; SAD = single ascending dose; $t_{1/2}$ = apparent terminal elimination half-life; TEAE = treatment-emergent adverse event; t_{max} = time of the maximum observed concentration; V_z/F = apparent volume of distribution.

Study Design

This will be a Phase 1, randomized, double-blind, placebo-controlled, single and multiple ascending dose trial to evaluate the safety, tolerability, and pharmacokinetics (PK) of AQ280 conducted at a single clinical site. An investigation of food effect will be included in the single dose administration part of the study.

The decision to proceed to the next dose group or trial part will be taken by the dose escalation committee (DEC). Dose increases between groups may be up to 5-fold for dose levels where the next dose is predicted not to surpass exposure limits of 35 ng/mL (maximum observed concentration [C_{max}]) or 303 ng/mL*h (area under the concentration-time curve [AUC]), ie, exposures corresponding to the predicted minimally pharmacologically active dose of 10 mg; but will not be more than 3-fold at any subsequent dose increment.

Part A: Single ascending dose (SAD)

Five sequential dose groups with single administration of AQ280 capsule are planned, with 1 group including a second treatment period with dose administration under fed condition to investigate food interaction. Sentinel dosing will be used in the first dose group.

The single ascending dose (SAD) portion will include:

- A screening visit from 2 days up to 5 weeks before the dose of investigational medicinal product (IMP).
- An in-clinic treatment period of 4 days which includes a 48-hour period after the dose. Eligible subjects will be randomized on Day 1 to AQ280 or placebo prior to administration.
- A safety follow-up phone call will be conducted 1 week (±2 days) after dose administration.

Dose administration will occur on Day 1.

Safety assessments will include adverse event (AE) reporting, vital signs, electrocardiograms (ECGs), clinical laboratory tests, and physical examination.

Blood samples to determine the PK of AQ280 and its main metabolite, AQ282, will be collected from predose up to 48 hours postdose.

Part B: Multiple ascending dose

Three sequential dose groups are planned, with subjects dosed once daily (QD).

The multiple ascending dose (MAD) portion will include:

- A screening visit from 2 days up to 5 weeks before the first dose of IMP.
- An in-clinic treatment period of 9 days which includes a 48-hour period after the last dose. Eligible subjects will be randomized on Day 1 to AQ280 or placebo prior to administration.
- A safety follow-up visit will be conducted 1 week (±3 days) after the final dose.

For all subjects, dosing is planned to be QD on Days 1 to 7, inclusive, at approximately the same time each morning. The total daily dose administered will not exceed an exposure shown to be safe and well tolerated in Part A.

Safety assessments will include AE reporting, vital signs, ECGs, clinical laboratory tests, and physical examination.

Blood samples to determine the PK of AQ280 and its main metabolite, AQ282, will be collected from predose up to 24 hours postdose on Day 1; predose on Days 3 through 6; and from predose up to 48 hours postdose on Day 7.

Number of Subjects

Each group will have 8 subjects, randomized 6:2 to AQ280:placebo.

For Part A, the total will be approximately 40 subjects (8 subjects × 5 groups).

For Part B, the total will be approximately 24 subjects (8 subjects × 3 groups).

Additional groups may be utilized based on the need for more evaluations or groups may be removed based on data obtained.

Diagnosis and Main Criteria for Inclusion

The trial subject population are healthy subjects, male or female, 18 to 65 years, inclusive. Each group should contain both male and female subjects, preferably at least 2 subjects of each gender.

Furthermore, subjects with history of any significant infectious disease are excluded to mitigate the potential risk of infection. Light smoking during the trial is permitted, as this is not expected to interfere with AQ280.

Investigational Medicinal Products, Dose, and Mode of Administration

AQ280 capsule:

- Active substance: AQ280
- Dose form: capsule, hard
- Strength: 3 to 100 mg (dosage strength expressed as the free base moiety of AQ280)
- Start dose: 3 mg
- Method of administration: oral.

Reference Product and Mode of Administration

Placebo capsule:

- Active substance: none
- Dose form: capsule, hard
- Strength/dose: not applicable
- Method of administration: oral.

Duration of Subject Participation in the Study

Part A: up to approximately 6 weeks, including screening and safety follow-up. For the food effect evaluation group, up to approximately 8 weeks, including screening and safety follow-up.

Part B: up to approximately 7 weeks, including screening and safety follow-up.

Statistical Methods

Safety

Adverse events will be summarized for all treated subjects (safety analysis set) and will be presented by Medical Dictionary for Regulatory Activities preferred term and primary system organ class, and by group and treatment as the number of AEs and the number (percentage) of subjects with AEs. The percentage of subjects with AEs will be compared between treatments by a chi-square test or Fisher's exact test.

Vital signs, ECG, and laboratory parameters will be summarized by descriptive statistics (actual values and changes from baseline) at each assessment timepoint by group and treatment and by shift tables (according to normal ranges).

Pharmacokinetics

Plasma concentrations and PK parameters of AQ280 and its main metabolite, AQ282, will be listed and summarized by descriptive statistics per dose group and (for Part B only) day. Concentration-time profiles will be generated per dose group.

In Part A, where data are available, AQ280 dose proportionality will be examined across groups. The PK parameters AUC from time 0 extrapolated to infinity ($AUC_{0-\infty}$), AUC from time 0 to the time of the last quantifiable concentration ($AUC_{0-tlast}$), and C_{max}, will be analyzed for dose proportionality using a power model approach or analysis of variance (ANOVA) model as appropriate. Where data are available, the effect of food at 1 dose level in Part A will be investigated using ANOVA.

In Part B, the PK parameters AUC over a dosing interval (AUC_{τ}) and C_{max}, on Day 7 will be analyzed for dose proportionality using a power model approach or ANOVA model as appropriate.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve from time 0 extrapolated to infinity
AUC_{0-12}	area under the concentration-time curve over the time interval 0 to 12 hours postdose
AUC_{0-24}	area under the concentration-time curve over the time interval 0 to 24 hours postdose
$AUC_{0-tlast}$	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
AUC_{τ}	area under the concentration-time curve over a dosing interval
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CRO	contract research organization
CYP	cytochrome P450
DEC	dose escalation committee
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EoE	eosinophilic esophagitis
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HED	human equivalent dose
ICF	informed consent form
ICH	International Conference on Harmonisation
IL	interleukin
IMP	investigational medicinal product
JAK	Janus kinase
MAD	multiple ascending dose
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 method
SAD	single ascending dose
SAE	serious adverse event
TMF	trial master file
ULN	upper limit of normal

1. INTRODUCTION

1.1. Overview

AQ280 is a highly selective inhibitor of Janus kinase (JAK) 1 that is being developed primarily for oral treatment of eosinophilic esophagitis (EoE). AQ280 blocks the signalling pathways of several cytokines including the interleukins (ILs) IL-4, IL-9, IL-13, IL-15 as well as thymic stromal lymphopoietin, which are considered key cytokines in the pathogenesis of EoE and many other immune-related diseases.

1.2. Summary of Nonclinical Pharmacology

AQ280 has been shown to inhibit JAK1 activity in a range of in vitro and in vivo assays, demonstrating its potency in inhibiting phosphorylation of tyrosine kinase substrates and activation of signal transducer and activator of transcription molecules. CCI

1.3. Summary of Safety Pharmacology

CCI

1.4. Summary of Toxicology

CCI

CCI

[redacted]

1.5. Summary of Nonclinical Pharmacokinetics

CCI

[redacted]

CCI

[redacted]

Table 1: No Observed Adverse Effect Level Across Studies in Mice and Dogs

Study duration	Dose (mg/kg/day)	HED (mg)	C_{max} (ng/mL)	AUC (ng/mL*h)	Dose limiting findings
Mice					
CCI [redacted]					
Dog					
CCI [redacted]					

Abbreviations: AUC = area under the concentration-time curve; C_{max} = maximum observed concentration; F = female; HED = human equivalent dose; M = male; NOAEL = no observed adverse effect level.

C
C [redacted]

1.6. Summary of Clinical Experience

AQ280 has not yet been tested in humans.

1.7. Study Rationale

This is the first time AQ280 will be administered to humans. The principal aim of this study is to obtain safety and tolerability data when AQ280 is administered orally as single and multiple doses to healthy subjects. This information, together with the pharmacokinetic (PK) data, will help establish the doses and dosing regimen suitable for future studies in patients. The effect of AQ280 on selected biomarkers will also be investigated. The study will also investigate the effects of food on the PK of AQ280 prior to patient studies.

1.8. Benefit-risk Assessment

Healthy subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study. The risks of participation are primarily those associated with adverse reactions to the study treatment, although there may also be some discomfort from collection of blood samples and other study procedures. More information about the known and expected benefits, risks, and reasonably anticipated adverse events (AEs) associated with AQ280 may be found in the investigator's brochure.[1]

2. OBJECTIVES AND ENDPOINTS

The objectives and endpoints of the study are presented in Table 2.

Table 2: Objectives and Endpoints

Objectives	Endpoints
Primary:	
• to evaluate the safety and tolerability of single and multiple ascending oral doses of AQ280, and to determine a safe therapeutic range of AQ280 in healthy subjects	• number of TEAEs per subject • clinically significant abnormalities in vital signs (systolic and diastolic blood pressure, pulse rate, and oral body temperature) • abnormal ECG (QTcF interval of >450 msec for males and >470 msec for females, or change from baseline of >30 msec) measured from Day 1 (postdose) up until 48 hours postdose in Part A and up to the follow-up visit in Part B • clinically significant changes in laboratory evaluations
Secondary:	
• to determine the PK of AQ280 after single and multiple oral doses • to determine the PK of the AQ280 main metabolite, AQ282, after single and multiple oral doses • to determine the effect of food on the PK of AQ280 after single oral dose	Part A (SAD): • primary PK parameters derived from plasma concentration-time profile of AQ280: $AUC_{0-\infty}$, C_{max} ($AUC_{0-tlast}$ may be included as a primary PK parameter if $AUC_{0-\infty}$ cannot be calculated) • primary PK parameters derived from plasma concentration-time profile of the AQ280 main metabolite, AQ282: $AUC_{0-\infty}$, C_{max} ($AUC_{0-tlast}$ may be included as a primary PK parameter if $AUC_{0-\infty}$ cannot be calculated) • comparison of the primary PK parameters of AQ280 after single dose administration in the fasted state and in the fed state Part B (MAD): • primary PK parameters derived from plasma concentration-time profile of AQ280 on Day 1 and Day 7: AR, AUC_{τ}, C_{max} • primary PK parameters derived from plasma concentration-time profile of the AQ280 main metabolite, AQ282, on Day 1 and Day 7: AUC_{τ}, C_{max}

Objectives	Endpoints
Exploratory:	
[redacted]	C CI [redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

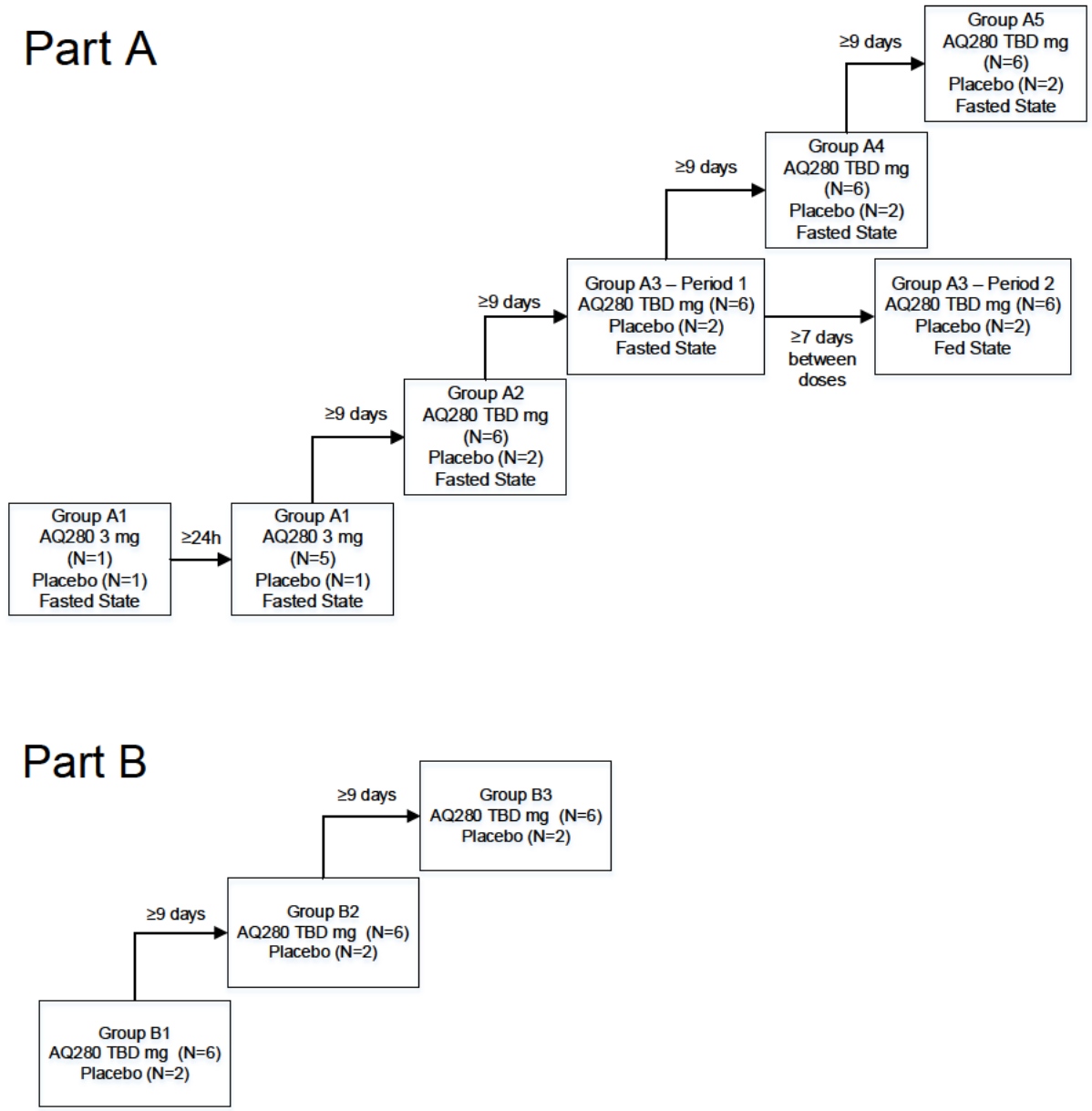
Abbreviations: AR = accumulation ratio; $AUC_{0-\infty}$ = area under the concentration-time curve from time 0 extrapolated to infinity; $AUC_{0-tlast}$ = area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; AUC_{τ} = area under the concentration-time curve over a dosing interval; CL/F = apparent total clearance; C_{max} = maximum observed concentration; CCI
ECG = electrocardiogram; CCI
MAD = multiple ascending dose;
PD = pharmacodynamic; PK = pharmacokinetic(s); QTcF = QT interval corrected for heart rate using Fridericia's method; SAD = single ascending dose; $t_{1/2}$ = apparent terminal elimination half-life; TEAE = treatment-emergent adverse event; t_{max} = time of the maximum observed concentration; V_z/F = apparent volume of distribution.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This will be a Phase 1, randomized, double-blind, placebo-controlled, single and multiple ascending dose trial to evaluate the safety, tolerability, and PK of AQ280. An investigation of food effect will be included in the single dose administration part of the study. The study will be conducted in 2 parts – Part A, single ascending dose (SAD) evaluations, including food effect, and Part B, multiple ascending dose (MAD) evaluations. Schematics of the planned groups for each part are presented in Figure 1.

Figure 1: Planned Groups (Parts A and B)



Abbreviations: N = number of subjects; TBD = to be determined.

3.1.1. Part A (Single Ascending Dose)

Part A will comprise a single-dose, sequential group, escalating-dose design conducted in healthy adult male and female subjects; also incorporating a single-group, 2-period crossover arm investigating the effect of dosing AQ280 with food compared to dosing in the fasting condition. The first dose level administered is planned to be 3 mg AQ280.

A total of approximately 40 subjects are planned to be studied in 5 groups (Groups A1 to A5; with one of the groups including the food effect evaluation). In each group, 6 subjects will receive AQ280 and 2 subjects will receive placebo. The dose will be administered in the fasted state in accordance with the randomization schedule on the morning of Day 1 for all groups, including Period 1 for the food effect evaluation group (see Section 3.1.1.1 for additional food-evaluation group requirements). Each group should contain both male and female subjects, preferably at least 2 subjects of each gender. Additional groups may be added based on the need for more evaluations or groups removed based on data obtained.

The first group in Part A will be divided into 2 cohorts, with each cohort being dosed at least 24 hours apart. The first cohort will comprise 2 subjects, with 1 subject receiving AQ280 and 1 subject receiving placebo. The second cohort will comprise 6 subjects, with 5 subjects receiving AQ280 and 1 subject receiving placebo. The 2 sentinel subjects (first cohort) will be dosed at least 24 hours before the second cohort of 6 subjects. Dosing of subjects in the second cohort will not occur if any of the dose escalation stopping criteria (Section 3.7) are met by the 2 sentinel subjects. Circumstances under which sentinel dosing may be introduced in other groups are detailed in Section 3.4.1.

There will be a minimum of 9 days between dose escalations for each group.

Potential subjects will be screened to assess their eligibility to enter the study from 2 days up to 5 weeks before the dose of AQ280 or placebo. Each subject will participate in 1 group only and will reside at the study site from Day -1 (the day before dosing) to Day 3 of the treatment period, with dose administration occurring on Day 1. A safety follow-up phone call will be conducted 1 week (±2 days) after dosing.

Each eligible subject will participate in 1 treatment period only, except for the food effect group, where each subject will participate in 2 treatment periods.

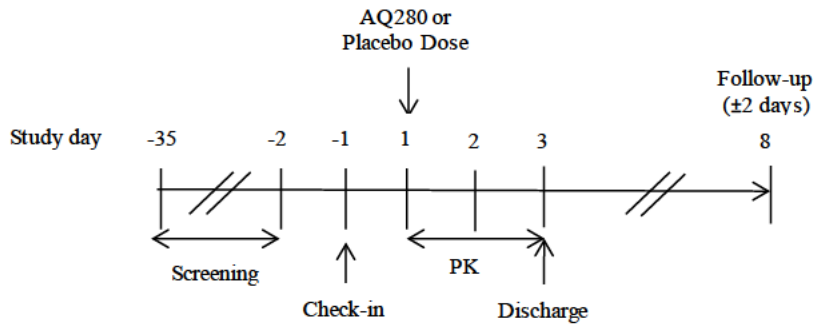
Based on the ongoing review of the safety, tolerability, and PK results, additional outpatient visits may be required.

Safety assessments will include AE reporting, vital signs, electrocardiograms (ECGs), clinical laboratory tests, and physical examination.

Blood samples to determine the PK of AQ280 and its main metabolite, AQ282, will be collected from predose up to 48 hours postdose.

An overview of the study design for Part A is shown in Figure 2.

Figure 2: Study Schematic (Part A)



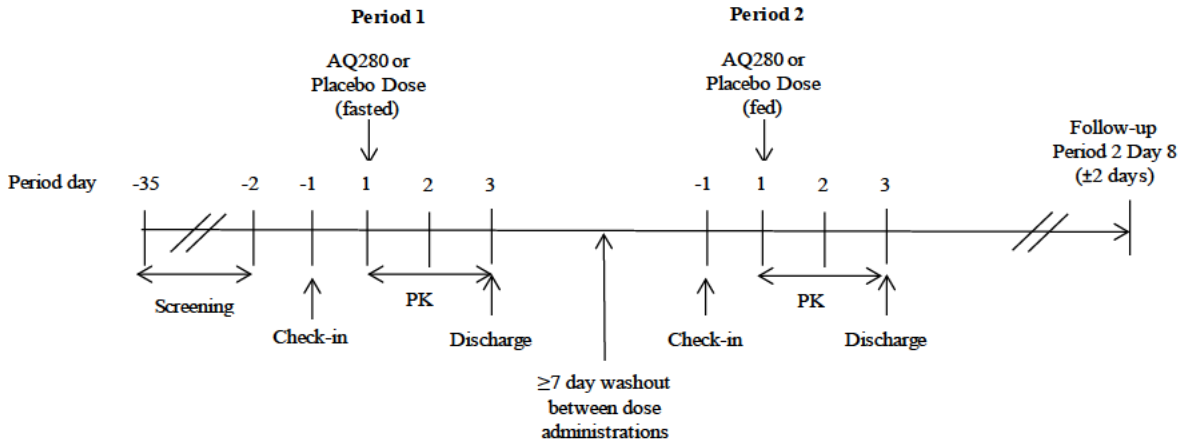
Abbreviation: PK = pharmacokinetics.

3.1.1.1. Food Effect Evaluation

Subjects in the food effect evaluation group will participate in 2 treatment periods, with the same treatment (AQ280 or placebo) administered in both periods. Period 1, Day 1 dose will be administered in the fasted state in accordance with a randomization schedule and Period 2, Day 1 dose will be given 30 minutes after starting a standard high-fat breakfast (see Section 6.2). The dose administrations in the 2 treatment periods will be separated by a washout of ≥7 days.

An overview of the study design for Part A, food effect evaluation, is shown in Figure 3.

Figure 3: Study Schematic (Part A, Food Effect Evaluation)



Abbreviation: PK = pharmacokinetics.
Note: If conduct of Period 2 is delayed, a safety follow-up phone call may be done 1 week (±2 days) after dosing in Period 1.

The total duration of study participation for each subject (from screening through safety follow-up visit) is anticipated to be approximately 6 weeks. For the food effect evaluation group, up to approximately 8 weeks, including screening and safety follow-up, is anticipated for each subject.

Schedules of Assessments for Part A and for Part A food effect evaluation are presented in Appendix 6.

3.1.2. Part B (Multiple Ascending Dose)

Part B will comprise a multiple-dose, sequential group, escalating-dose design conducted in healthy adult male and female subjects. Part B may start prior to completion of all planned dose groups in Part A, at a dose equal to or less than that evaluated as safe and well tolerated in Part A.

A total of approximately 24 subjects are planned to be studied in 3 groups (Groups B1 to B3). In each group, 6 subjects will receive AQ280 and 2 subjects will receive placebo. Each group should contain both male and female subjects, preferably at least 2 subjects of each gender. Additional groups may be added based on the need for more evaluations or groups removed based on data obtained.

There will be a minimum of 9 days between dose escalations for each group.

Potential subjects will be screened to assess their eligibility to enter the study from 2 days up to 5 weeks before the first dose of AQ280 or placebo. Each subject will participate in 1 group only and reside at the study site from Days -1 to 9.

For all subjects, dosing is planned to be QD on Days 1 to 7, inclusive, at approximately the same time each morning. The dosing regimen in Part B may be changed following review of preliminary data from groups in Part A or previous groups in Part B. The daily dose administered, when given repeatedly, will be predicted to not exceed an exposure shown to be safe and well tolerated in Part A. Dietary state will be determined based on data obtained in Part A.

A safety follow-up visit will be conducted 1 week (±3 days) after the final dose.

Based on the ongoing review of the safety, tolerability, and PK results, additional outpatient visits may be required.

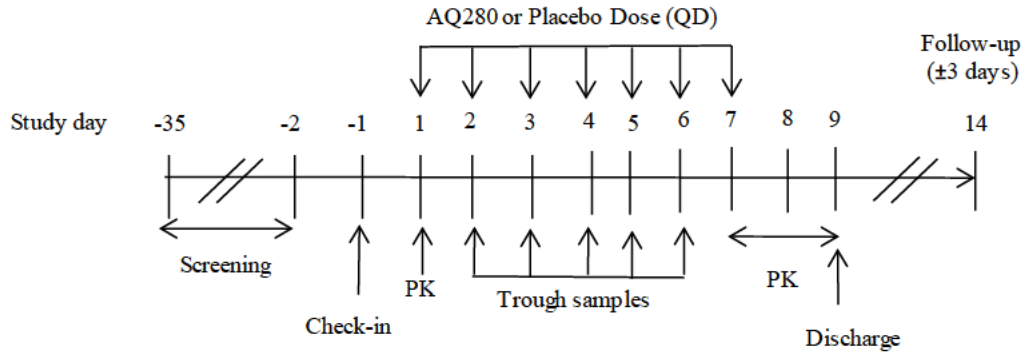
Safety assessments will include AE reporting, vital signs, ECGs, clinical laboratory tests, and physical examination.

Blood samples to determine the PK of AQ280 and its main metabolite, AQ282, will be collected from predose up to 24 hours postdose on Day 1; predose on Days 3 through 6; and from predose up to 48 hours postdose on Day 7.

Urine samples will be collected at intervals for the purpose of metabolite profiling.

An overview of the study design for Part B is shown in Figure 4.

Figure 4: Study Schematic (Part B)



Abbreviations: PK = pharmacokinetics; QD = once daily.

The total duration of study participation for each subject (from screening through follow-up visit) is anticipated to be approximately 7 weeks.

A Schedule of Assessments is presented in Appendix 6.

3.2. Study Start and End of Study Definitions

The start of the study is defined as the date the first subject signs an informed consent form (ICF). The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

3.3. Additional Groups

Following review of the safety, tolerability, and PK data, additional dose groups (where systemic exposure is not expected to exceed that stated in the dose escalation stopping criteria [Section 3.7]) may be added to the study. Up to 3 further groups of 8 subjects (6 active:2 placebo) may be included in each of Parts A and B. There will be no further dose escalation in these additional groups if dose escalation stopping criteria have been met, and a dose level cannot be repeated if it previously met a stopping criterion. The requirement for additional groups will be agreed with the sponsor and dose escalation committee (DEC) and documented in the trial master file (TMF).

3.4. Discussion of Study Design, Including the Choice of Control Groups

For both parts of the study, a sequential group, ascending dose design has been chosen for safety reasons as AQ280 is in the early stages of clinical development, with Part A of the study being the first time it will be administered to humans. Oral doses have been chosen for both parts of the study, as this is the intended clinical route of administration. A 2-period crossover design has been chosen for the food effect evaluation, as this gives a within-subject assessment of the influence of food on the PK of AQ280 and so increases the power of the study for the given number of subjects.

It is the intent of Part B to dose subjects such that steady state plasma levels of AQ280 are achieved and maintained for several days. Based on the available nonclinical data, it is expected that this will be achieved within 7 days of QD dosing; however, a full review of all available safety, tolerability, and PK data from Part A will be performed to confirm the dose

regimen for Part B. If the apparent terminal elimination half-life ($t_{1/2}$) of AQ280 is shorter or longer than predicted by the nonclinical data, further dose escalation may be required to include a revised dose regimen. This revised dose regimen will be agreed upon by the sponsor and DEC.

Details of the dosing regimen and duration used for Part B of the study will be documented in the TMF.

A 48-hour period of residency after single dose in Part A and final dose in Part B is expected to correspond to [redacted] half-lives of AQ280.

Based upon the nonclinical data, the duration of each treatment period is considered adequate to achieve the study objectives. An interval of at least 7 days between dose administrations in the 2 treatment periods in the food effect evaluation is considered adequate to prevent carryover of AQ280.

This study will be double blind and placebo controlled in order to avoid bias in the collection and evaluation of data during its conduct. Placebo has been chosen as the control treatment to assess whether any observed effects are treatment related or simply reflect the study conditions.

Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications. Subjects with history of any significant infectious disease are excluded to mitigate the potential risk of infection. Light smoking during the trial is permitted, as this is not expected to interfere with AQ280.

3.4.1. Dose Interval

Following thorough review of all available nonclinical data (pharmacological and toxicological), dosing for the starting dose level in Part A (Group A) will be such that 2 subjects (1 AQ280 and 1 placebo) will be dosed at least 24 hours before the remaining 6 subjects.

At least 3 JAK inhibitors are approved for clinical use and several others are in Phase 3 clinical development. Thus, the risk of on-target suspected unexpected serious adverse reactions will be negligible. To minimize the consequence of any potential unknown off-target toxicity, sentinel dosing will be implemented for the first SAD group in Part A. Based on knowledge of the pharmacodynamic (PD) effects of other JAK inhibitors, in particular the JAK1-selective inhibitor abrocitinib, no effects are expected from a single dose beyond 24 hours after dosing. Therefore, a 24-hour interval between dosing of the sentinel subjects and the remaining subjects in the first group is considered sufficient, after review of available safety data.

Because of the well described target pharmacology and safety of other JAK inhibitors, sentinel dosing is not considered necessary for Part B, in which the predicted exposure will not exceed an exposure already shown to be safe and well tolerated in Part A.

Sentinel dosing may be introduced in other groups than in the first SAD group under the following circumstances:

- In case of any emerging clinical signs or AEs that do not meet stopping criteria but in the opinion of the DEC warrant a more cautious dose escalation.
- In case of non-linear PK that warrants a more cautious dose escalation.
- If the exposure is expected to exceed the NOAEL exposure in dogs, in which case further dose escalation will require a substantial protocol amendment.

3.5. Selection of Doses in the Study

3.5.1. Starting Dose for Single Ascending Dose

The lowest dose (AQ280 3 mg) is approximately [redacted]-fold below the human equivalent dose (HED) to the NOAEL in dogs ([redacted] mg/kg/day), the most sensitive species tested. Based on a conversion factor of 1.8 (dog to human), the HED is [redacted] mg/kg, corresponding to [redacted] mg for a person weighing 60 kg.[2] Using a safety factor of [redacted] gives a maximum recommended starting dose of [redacted] mg. As [redacted] mg is expected to give a C_{max} exceeding the unbound concentration that caused [redacted] inhibition of IL-4 in human whole blood, which could result in a pharmacological effect, the starting dose will be 3 mg. The predicted exposure at 3 mg, based on animal PK and hepatocyte clearance data across species, including man, is [redacted]-fold (C_{max}) and [redacted]-fold (AUC) below the exposure at NOAEL in dogs.

Dose increases between groups may be up to 5-fold for dose levels where the next dose is predicted not to surpass exposure limits of 35 ng/mL (C_{max}) or 303 ng/mL*h (AUC), ie, exposures corresponding to the predicted minimally pharmacologically active dose of 10 mg; but will not be more than 3-fold at any subsequent dose increment. Exposures will be planned to not exceed that stated in the dose escalation stopping criteria (Section 3.7). Exposure will be assumed to increase in a dose-proportional manner until there are sufficient PK data available to suggest PK is not linear.

3.5.2. Starting and Maximum Dose for Multiple Ascending Dose

The starting dose for MAD (Part B) will be the lowest dose generating exposures within the pharmacologically active range. Each MAD group will be initiated only after review of safety data from a SAD group of the same or higher dose level shows that it is safe to proceed. Thus, the highest daily dose in the MAD part will give an exposure not expected to exceed an exposure shown to be safe and well tolerated in the SAD part.

Multiple ascending doses will not be more than 3-fold at any subsequent dose increment.

Details of all doses administered in Parts A and B of the study will be documented in the TMF.

3.6. Dose Escalation

Doses will be administered in an escalating manner following satisfactory review by the sponsor and investigator of the safety and tolerability data (up to 48 hours postdose) and plasma PK data (up to 48 hours postdose) from the lower dose levels. Doses may be reduced and may be lower than the starting dose. There will be a minimum of 9 days between dose escalations to allow sufficient time for an adequate safety review.

Dose escalation in both Parts A and B will only occur if data from a minimum of 6 subjects have been reviewed from the previous lower dose group, such that data from a minimum of 4 subjects who have received AQ280 will be used to make the dose escalation decision.

The justification for this is as follows:

- The study treatment is of a known pharmacological class for which the on-target effects in humans are well characterized. Based upon nonclinical data, no clinically important off-target effects are expected within the proposed dose range.
- A minimum of 4 subjects receiving the active drug is considered sufficient to characterize the safety profile and PK/PD response to AQ280.

Prior to each dose escalation, the DEC, composed of the investigator, medical monitor, and sponsor medical representative as voting members and supported by additional team members (eg, pharmacokineticist) will review all available data in a blinded manner to ensure it is safe to proceed with the next planned dose level. An interim safety report, summarizing results from all available safety assessments, will be provided to the DEC prior to the dose escalation meeting. Any clinically significant results will be discussed by the DEC before dose escalation continues. Available interim PK data will also be reviewed to confirm that the study design remains appropriate. In the event of a disagreement between DEC voting members on the dose escalation decision, the decision of the investigator will be upheld.

3.7. Dose Escalation Stopping Criteria

The study will be halted if 1 or more subjects experience a serious adverse event (SAE) that is considered to be related to investigational medicinal product (IMP) or 2 or more subjects in the same group experience severe AEs that are considered to be related to IMP. If, following an internal safety review, the sponsor deems it appropriate to restart the study, this can be done following approval of a substantial protocol amendment. Dosing of subjects, including any ongoing multiple dose groups, will be stopped immediately if any of the dose escalation stopping criteria are met.

In Parts A and B, following consultation with the sponsor and DEC, dose escalation will stop if:

- Clinically significant abnormal signs or symptoms of similar nature occur in 2 or more subjects in a group that, in the opinion of the investigator, warrant stopping of dose escalation.
- There is evidence of clinically significant increases in liver function tests defined as 3 × upper limit of normal (ULN) for aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, or gamma-glutamyl transferase or 2 × ULN for total bilirubin in 2 or more subjects in a group (confirmed with repeat testing).
- Clinically significant increases in serum creatinine, defined as 1.5 × ULN (confirmed with repeat testing), in 2 or more subjects in a group.
- Hemoglobin decrease of >3.5 g/dL compared to Day -1 levels (confirmed by repeat testing) in 2 or more subjects in a group.

- Neutrophil count <1.5 x 10^9/L and/or a platelet count <100 x 10^9/L (confirmed with repeat testing) in 2 or more subjects in a group.
- Clinically significant increases in activated partial thromboplastin time or prothrombin time, defined as 2 × ULN (confirmed by repeat testing) in 2 or more subjects in a group.
- The systemic exposure of AQ280 is predicted to exceed a C_{max} of CCI ng/mL (based on C mg/kg/day dose in males and females in 4-week dog study) and/or an AUC of CCI ng/mL*h (based on 5 mg/kg/day dose in males in 16-week dog study) in any individual subject; ie, systemic exposure will be no greater than the exposure at NOAEL in the most sensitive species.
- QT interval corrected for heart rate using Fridericia's method (QTcF) increases >60 ms compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values >500 ms (confirmed with repeat testing) in 1 or more subjects in a group.

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria at the screening visit (and/or at check-in, where noted):

1. Males or females, of any race, between 18 and 65 years of age, inclusive.
2. Body mass index between 18.0 and 32.0 kg/m^2, inclusive.
3. In good health, determined by no clinically significant findings from medical history, 12-lead ECG, vital sign measurements, and clinical laboratory evaluations at screening and check-in and from the physical examination at check-in, as assessed by the investigator (or designee).
4. Females will not be pregnant or lactating, and females of childbearing potential and males will agree to use contraception as detailed in Appendix 4.
5. Able to comprehend and willing to sign an ICF and to abide by the study restrictions.

4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria at the screening visit (or at check-in, where noted):

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 any surgical (eg, stomach or intestinal surgery or resection) or medical condition that would potentially alter absorption, distribution, metabolism, and/or excretion of orally administered drugs. Uncomplicated appendectomy and hernia repair will be allowed. Cholecystectomy will not be allowed.
4. History of any significant infectious disease, as assessed by the investigator, within 2 weeks prior to the first dose of IMP.
5. AST and/or ALT values >1.2 × ULN.
6. Congenital nonhemolytic hyperbilirubinemia (including suspicion of Gilbert's syndrome).
7. Hemoglobin value, neutrophil count, and/or lymphocyte count <lower limit of normal.
8. Clinically significant abnormal ECG at screening or check-in.
9. Positive hepatitis panel and/or positive human immunodeficiency virus test (Appendix 2). Subjects whose results are compatible with prior immunization may be included at the discretion of the investigator
10. Current active tuberculosis based on Quantiferon™ tuberculosis Gold test.

Prior/concomitant therapy

11. Administration of a coronavirus disease 2019 vaccine in the past 30 days prior to the first dose of IMP.
12. 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 the first dose of IMP, unless deemed acceptable by the investigator (or designee).
13. Use or intend to use any prescription medications/products other than hormone replacement therapy, oral, implantable, transdermal, injectable, or intrauterine contraceptives within 14 days prior to the first dose of IMP, unless deemed acceptable by the investigator (or designee).
14. Use or intend to use slow-release medications/products considered to still be active within 14 days prior to check-in, unless deemed acceptable by the investigator (or designee).
15. Use or intend to use any nonprescription medications/products including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations within 7 days prior to check-in, unless deemed acceptable by the investigator (or designee).

Prior/concurrent clinical study experience

16. Participation in a clinical study involving administration of an investigational drug (new chemical entity) in the past 90 days prior to dosing.
17. Have previously completed or withdrawn from this study.

Diet and lifestyle

18. Alcohol consumption of >21 units per week for males and >14 units for females. One unit of alcohol equals ½ pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits.

19. Positive alcohol breath test result or positive urine drug screen (confirmed by repeat) at screening or check-in.
20. History of alcoholism or drug/chemical abuse within 2 years prior to check-in.
21. Smoking >5 cigarettes per day, on average, or use the equivalent tobacco- or nicotine-containing products per day.
22. Ingestion of poppy seed-, Seville orange-, star fruit-, or grapefruit-containing foods or beverages within 7 days prior to check-in.

Other exclusions

23. Receipt of blood products within 2 months prior to check-in.
24. Donation of blood from 3 months prior to screening, plasma from 2 weeks prior to screening, or platelets from 6 weeks prior to screening.
25. Poor peripheral venous access.
26. Subjects who, in the opinion of the investigator (or designee), should not participate in this study.

4.3. Subject Number and Identification

Subjects will have a unique identification number used at screening. Subjects will be assigned a subject number at the time of their randomization. Assignment of subject numbers will be in ascending order (eg, in Part A Subjects 0101, 0102, etc, in Part B Subjects 0201, 0202, etc). Replacement subjects (Section 4.4) will be assigned a subject number corresponding to the number of the subject he/she is replacing plus 1000 (eg, Subject 1101 replaces Subject 0101).

Subjects will be identified by screening identification number or subject number only on all study documentation. A list identifying the subjects by subject number will be kept in the Site Master File.

4.4. Subject Withdrawal and Replacement

A subject is free to withdraw from the study at any time. In addition, a subject will be withdrawn if any of the following criteria are met:

- change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects subject safety as determined by the investigator (or designee)
- noncompliance with the study restrictions that might affect subject 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 subject withdrawal.

If a subject is withdrawn from dosing, the sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic case report form (eCRF). If a subject is withdrawn from the study, efforts will be made to perform all follow-up assessments, if possible (Appendix 6). Other applicable safety-related procedures may be performed at the investigator's (or designee's) and/or sponsor's discretion. If the subject is in-house, these procedures should be performed before the subject is discharged from the

clinic. The investigator (or designee) may also request that the subject return for an additional follow-up phone call or visit. All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the investigator (or designee) to have stabilized.

Subjects who are withdrawn for reasons not related to study treatment may be replaced following discussion between the investigator and the sponsor. Subjects withdrawn as a result of AEs thought to be related to the study treatment will generally not be replaced.

4.5. Study Termination

The study may be discontinued if any of the following criteria are met:

- potential or actual violation of Applicable Law, patient safety or scientific standards of integrity (including breach or insolvency by any party), as decided by investigator or sponsor
- medical or ethical reasons affecting the continued performance of the study, as decided by the investigator, sponsor, or sponsor's medical monitor
- cancelation of drug development, as decided by sponsor.

5. STUDY TREATMENTS

5.1. Description, Storage, Packaging, and Labeling

Active pharmaceutical ingredient will be supplied by the sponsor (or designee) for extemporaneous preparation of the IMP, along with the batch/lot numbers and certificates of analysis. The IMPs (3 to 100 mg AQ280 hard capsules and placebo capsules) will be manufactured by Labcorp Drug Development and a certificate of release authorized by a qualified person from the United Kingdom will be issued for the IMP. The dosage strength is expressed as free base moiety of AQ280. Placebo capsules will contain microcrystalline cellulose. Excipients fulfil the specifications according to the European Pharmacopoeia.

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All IMPs will be stored at the study site in a location that is locked with restricted access.

The AQ280 and placebo capsules will be packaged in bottles with twist-off polypropylene caps, labelled for each subject. The bulk drug container and unit dose containers will be labeled in accordance with national laws and regulations. The IMPs will be transferred from bulk supplies into the subject's dose container by qualified clinical staff.

5.2. Study Treatment Administration

Each dose of AQ280 and placebo will be administered orally with approximately 240 mL of room temperature water. In Parts A and B, all doses will be administered after an overnight fast of at least 10 hours, with the exception of the food effect evaluation group in Part A, where the dose given in Treatment Period 2 will be administered 30 minutes after starting a high-fat breakfast.

Subjects will be dosed in numerical order while seated and will not be permitted to lie supine for 2 hours after dosing, except as necessitated by the occurrence of an AE(s) and/or study procedures.

5.3. Randomization

The randomization code will be produced by the statistics department at Labcorp Drug Development using a computer-generated pseudo-random permutation procedure.

In Parts A and B, 2 subjects in each group will be randomly assigned to receive placebo.

For the first group in Part A (Group A1), sentinel dosing will occur whereby 2 subjects (1 active and 1 placebo) will be dosed on 1 day and, providing no safety concerns arise, the remaining 6 subjects will be dosed at least 24 hours later.

Subjects in the food effect evaluation group in Part A will receive the same treatment in Treatment Periods 1 and 2.

5.4. Blinding

The following controls will be employed to maintain the double-blind status of the study:

- The placebo capsules will be identical in appearance to the AQ280 capsules.
- The investigator and other members of staff (with the exception of pharmacy staff and bioanalytical analysis staff) involved with the study will remain blinded to the treatment randomization code during the conduct of the study.
- Interim bioanalytical data will be provided to Labcorp Clinical Research Unit in a blinded manner.
- Where possible, PD data will be provided to Labcorp Clinical Research Unit in a blinded manner.

To maintain the blind, the investigator will be provided with a sealed randomization code for each subject, containing details of their treatment. These individual sealed envelopes will be kept in a limited access area that is accessible 24 hours a day. In order to manage subject safety or to support dose escalation decisions (in the event of possibly treatment-related SAEs or severe AEs), the decision to unblind resides solely with the investigator. Whenever possible, and providing it does not interfere with or delay any decision in the best interest of the subject, the investigator will discuss the intended code-break with the sponsor. If it becomes necessary to break the code during the study, the date, time, and reason will be recorded in the subject's source data and on the individual envelope and will be witnessed by a second person.

5.5. Treatment Compliance

The following measures will be employed to ensure treatment compliance:

- All doses will be administered under the supervision of suitably qualified study site staff.

- Immediately after dose administration, visual inspection of the mouth and hands will be performed for each subject.
- At each dosing occasion, a predose and postdose inventory of IMP will be performed on the dose containers.

5.6. Drug Accountability

The investigator (or designee) will maintain an accurate record of the receipt of the study supplies received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the sponsor upon request.

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 supplies will be returned to the sponsor or disposed of by the study site, per the sponsor's written instructions.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

Subjects will refrain from use of any prescription or nonprescription medications/products during the study until the follow-up phone call or visit, unless the investigator (or designee) and/or sponsor have given their prior consent.

Paracetamol/acetaminophen (2 g/day for up to 3 consecutive days), hormone replacement therapy, oral, implantable, transdermal, injectable, or intrauterine contraceptives are acceptable concomitant medications. The administration of any other concomitant medications during the study is prohibited without prior approval of the investigator (or designee), unless its use is deemed necessary for treatment of an AE. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data and in the eCRF.

6.2. Diet

While confined at the study site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities. Subjects will be fasted (at least 8 hours) before collection of blood samples for clinical laboratory evaluations.

On the days with intensive PK assessments (Day 1 for Part A and Days 1 and 7 for Part B), meals will be identical for each group with the exception of the high-fat breakfast for the food effect evaluation group.

On Day 1 in Part A, subjects will be fasted for at least 10 hours prior to dosing until approximately 4.5 hours after dosing, when lunch will be provided. With the exception of water given with the dose, subjects will not be allowed fluids from 1 hour prior to until

2 hours after dosing. Meals will be provided as appropriate at other times. Other than the fluid restrictions on dosing days, water will be freely available at all times.

Subjects in the food effect evaluation group in Treatment Period 2 will consume a high-fat breakfast (contents detailed in Table 3) before dosing. Subjects should start the meal 30 minutes prior to administration of the IMP. Study subjects should eat this meal in 30 minutes or less. The drug product should be administered 30 minutes after start of the meal.

Table 3: High-fat Breakfast Content

High-fat Breakfast
120 g fried eggs (2 eggs) in vegetable oil
50 g bacon (2 rashers)
72 g toasted white bread (2 slices)
13 g butter (2 pats)
108 g hash brown (3 each)
240 g whole milk
Total calories: 973 kcal

This high-fat meal contains the equivalent of approximately 150 protein calories, 250 carbohydrate calories, and 500 to 600 fat calories.

In Part B, the time interval between meals and dosing will be determined by the preliminary PK data from Part A and will be documented in the TMF. Meals will be provided as appropriate at other times. With the exception of water given with the dose, subjects will not be allowed fluids from 1 hour prior to dosing until 2 hours after dosing on the days with intensive PK assessments (Days 1 and 7) or until 1 hour after dosing on other days. Other than these fluid restrictions, water will be freely available at all times.

Foods and beverages containing poppy seeds, grapefruit, star fruit, or Seville oranges will not be allowed from 7 days prior to check-in until discharge in Part A and until the follow-up visit in Part B.

Caffeine-containing foods and beverages will not be allowed from 36 hours before check-in until discharge in Part A and until the follow-up visit in Part B.

Consumption of alcohol will not be permitted from 36 hours prior to check-in in Parts A and B until discharge in Part A. Up to 2 units/day of alcohol are permitted from discharge until 36 hours before the follow-up visit in Part B.

6.3. Smoking

Smoking will not be permitted from waking until after lunch on Day 1 (Part A) and on Days 1 and 7 (Part B), and for 1 hour before each blood pressure and pulse rate measurement outside these periods. Subjects will be permitted to smoke ≤5 cigarettes or equivalent tobacco- or nicotine-containing products per day outside of restricted times while they are resident at the study site.

6.4. Exercise

Subjects are required to refrain from strenuous exercise from 7 days before check-in until discharge in Part A and until the follow-up visit in Part B. If the investigator requests that a subject in Part A return to the study site for follow-up clinical laboratory assessment(s) or AE assessments, subjects will refrain from strenuous exercise until the requested follow-up visit(s). Subjects 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).

6.5. Blood Donation

Subjects 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 the follow-up phone call or visit.

7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The highest priority procedures will be performed closest to the nominal time. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- dosing
- blood samples (for AQ280 and its main metabolite, AQ282, assay)
- urine samples CCI [redacted]
- any other procedures.

7.1. Pharmacokinetic Assessments

7.1.1. Sample Collection and Processing

Blood samples will be collected by venipuncture or cannulation at the times indicated in the Schedules of Assessments in Appendix 6. The DEC may decide to alter the sampling schedule, allowing for up to 3 additional samples to be taken and up to 2 additional outpatient visits if additional samples beyond 48 hours postdose (but within 7 days post final dose) are required. The maximum volume of blood withdrawn per subject will not exceed the limit detailed in Appendix 3. Any changes to the scheduled times of PK assessments will be agreed with the sponsor and documented in the TMF. Samples taken from subjects who received placebo will be analyzed.

Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

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Procedures for collection, processing, and shipping of urine samples will be detailed in a separate document.

7.1.2. Analytical Methodology

Plasma concentrations of AQ280 and its main metabolite, AQ282, will be determined using a validated analytical procedure. Specifics of the analytical method will be provided in a separate document.

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7.2. Pharmacodynamic Assessments

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clinical chemistry or hematology panels, as applicable.

The timings of all PD assessments to be performed during the study are indicated in the Schedules of Assessments in Appendix 6 and may be subject to change based on the ongoing review of the data. Furthermore, up to 3 additional blood samples may be taken from each subject, with the maximum volume of blood withdrawn per subject not exceeding the limit detailed in Appendix 3. Any changes to the scheduled times of PD assessments will be agreed with the sponsor and documented in the TMF.

7.3. Safety and Tolerability Assessments

7.3.1. Adverse Events

Adverse event definitions, assignment of severity and causality, and procedures for reporting SAEs are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF to final discharge from the study. Subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as "How have you been feeling since you were last asked?", at least once each day while resident at the study site and at each study visit. Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the study.

Any AEs and remedial action required will be recorded in the subject's source data. The nature, time of onset, duration, and severity will be documented, together with an investigator's (or designee's) opinion of the relationship to study treatment.

Adverse events recorded during the course of the study will be followed up, where possible, until resolution or until the unresolved AEs are judged by the investigator (or designee) to have stabilized. This will be completed at the investigator's (or designee's) discretion.

7.3.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations at the times indicated in the Schedules of Assessments in Appendix 6. Clinical laboratory evaluations are listed in Appendix 2. The timing of clinical laboratory evaluations may be adjusted and/or additional clinical laboratory evaluations may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required.

Subjects will be asked to provide urine samples for drugs of abuse screen, and will undergo an alcohol breath test at the times indicated in the Schedules of Assessments in Appendix 6. For all female subjects, a pregnancy test will be performed and for postmenopausal females a follicle-stimulating hormone test will be performed at the times indicated in the Schedules of Assessments in Appendix 6.

An investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

7.3.3. Vital Signs

Supine blood pressure, supine pulse rate, and oral body temperature will be assessed at the times indicated in the Schedules of Assessments in Appendix 6. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

Day 1 predose blood pressure and pulse rate will be measured in triplicate at approximately 2-minute intervals. All subsequent measurements will be performed singly and repeated once if outside the relevant clinical reference ranges. Oral body temperature will be measured singly.

Subjects must be supine for at least 5 minutes before blood pressure and pulse rate measurements.

7.3.4. Electrocardiogram

7.3.4.1. 12-lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedules of Assessments in Appendix 6. Single 12-lead ECGs will be repeated once if either of the following criteria apply:

- QT interval corrected for heart rate using Fridericia's method (QTcF) value >500 ms
- QTcF change from the baseline (predose) is >60 ms.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

Day 1 predose 12-lead ECGs will be measured in triplicate at approximately 2-minute intervals. All subsequent measurements will be performed singly and repeated once if outside the relevant clinical reference ranges.

7.3.4.2. Telemetry

Cardiac rhythm will be monitored by telemetry at the times indicated in the Schedule of Assessments for Part A in Appendix 6.

Telemetry is not planned for Part B of the study but may be implemented if any clinically significant findings are identified in the data from Part A.

7.3.4.3. Continuous 12-lead Electrocardiogram Monitoring

Continuous 12-lead ECG monitoring using a digital recorder will take place at the times indicated in the Schedule of Assessments for Part A in Appendix 6.

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.

Subjects will be supine for at least 10 minutes before the extraction timepoint and for 5 minutes from the start of each extraction timepoint (each extraction will last for 5 minutes). Environmental distractions (eg, television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

When coinciding, vital sign assessments and PK sampling should always be performed after the ECG extraction time window. If a separate ECG machine is being used for safety assessments described in Section 7.3.4.1, that machine should be in place prior to the extraction window to permit safety ECGs to be recorded irrespective of the extraction window. If the machine is not in place prior to the extraction window, safety ECGs must be

recorded after the extraction window. If an integral system is used, safety ECGs may be recorded irrespective of the extraction window.

7.3.5. Physical Examination

A full physical examination or symptom-directed physical examination will be performed at the timepoints specified in the Schedules of Assessments in Appendix 6.

7.3.6. Body Weight

Body weight (in light clothing) will be recorded at the times indicated in the Schedules of Assessments in Appendix 6.

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

No formal statistical assessment, in terms of sample size, has been conducted as this is the first time AQ280 is being administered to humans. However, the number of subjects in each part of the present study is common in early clinical pharmacology studies and is considered sufficient to achieve the objectives of the study.

8.2. Analysis Populations

8.2.1. Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of active study treatment (AQ280) and have at least 1 valid PK concentration.

8.2.2. Pharmacodynamic Population

The PD population will include all subjects who received at least 1 dose of study treatment (AQ280 or placebo) and have at least 1 valid postdose PD assessment.

8.2.3. Safety Population

The safety population will include all subjects who received at least 1 dose of study treatment (AQ280 or placebo).

8.2.4. All Subjects Population

The all subjects population will include all subjects who signed the ICF and had any study assessment recorded in the database per the protocol.

8.3. Pharmacokinetic Analyses

Plasma concentrations of AQ280 and its main metabolite, AQ282, and plasma PK parameters will be listed and summarized by descriptive statistics per dose group and (for Part B only) day. Concentration-time profiles will be generated per dose group.

Pharmacokinetic parameters will be determined from plasma concentrations of AQ280 and its main metabolite, AQ282, using standard noncompartmental methods. Full details of PK parameters will be presented in the statistical analysis plan for this study.

In Part A, where data are available, AQ280 dose proportionality will be examined across groups. The PK parameters AUC from time 0 extrapolated to infinity ($AUC_{0-\infty}$), AUC from time 0 to the time of the last quantifiable concentration ($AUC_{0-tlast}$), and C_{max}, will be analyzed for dose proportionality using a power model approach or analysis of variance (ANOVA) model as appropriate. Where data are available, the effect of food at 1 dose level in Part A will be investigated using ANOVA.

In Part B, the PK parameters AUC over a dosing interval (AUC_{τ}) and C_{max}, on Day 7 will be analyzed for dose proportionality using a power model approach or ANOVA model as appropriate.

8.4. Pharmacodynamic Analyses

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

8.5. Safety Analysis

Adverse events will be summarized for all treated subjects (safety population) and will be presented by Medical Dictionary for Regulatory Activities preferred term and primary system organ class, and by group and treatment as the number of AEs and the number (percentage) of subjects with AEs. The percentage of subjects with AEs will be compared between treatments by a chi-square test or Fisher's exact test.

Vital signs, ECG, and laboratory parameters will be summarized by descriptive statistics (actual values and changes from baseline) at each assessment timepoint by group and treatment and by shift tables (according to normal ranges).

No formal statistical analysis of safety data is planned.

8.6. Interim Analysis

No formal interim analyses are planned for this study.

9. REFERENCES

1. AQ280 [Investigator's Brochure]. Place: Aqilion; Edition 1.0, Final 13 Apr 2022.

2. Food and Drug Administration. Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers [Internet]. Food and Drug Administration; 2005. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078932.pdf

10. APPENDICES

Appendix 1: Adverse Event Reporting

Definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject 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 a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study treatment, whether or not related to the study treatment.

Assessment of Severity

The investigator will be asked to provide an assessment of the severity of the AE using the following categories:

- **Mild**: Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate**: Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
- **Severe**: Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship to Study Treatment

The investigator (or designee) will make a determination of the relationship of the AE to the study treatment using a 4-category system according to the following guidelines:

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

Follow-up of Adverse Events

Every reasonable effort will be made to follow up with subjects who have AEs. Any subject who has an ongoing AE that is possibly related or related to the investigational medicinal product (IMP) or study procedures at the follow-up phone call or visit will be followed up, where possible, until resolution or until the unresolved AE is judged by the investigator (or

designee) to have stabilized. This will be completed at the investigator's (or designee's) discretion. Any subject who has an ongoing AE that is not related or unlikely related to the IMP or study procedures at the follow-up phone call or visit can be closed out as ongoing at the investigator's discretion.

Adverse Drug Reactions

All noxious and unintended responses to an IMP (ie, where a causal relationship between an IMP and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

For marketed medicinal products, a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function is to be considered an adverse drug reaction.

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, investigator's brochure for an unapproved IMP).

Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose either:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- results in a congenital anomaly/birth defect
- results in an important medical event (see below).

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Instances of death or congenital abnormality, if brought to the attention of the investigator at any time after cessation of the study treatment and considered by the investigator to be possibly related to the study treatment, will be reported to the sponsor.

<u>Definition of Life-threatening</u>

An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred (ie, does not include a reaction that might have caused death if it had occurred in a more serious form). For instance, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Definition of Hospitalization

Adverse events requiring hospitalization should be considered serious. In general, hospitalization signifies that the subject has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate at the study site. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered as serious.

Hospitalization for elective surgery or routine clinical procedures, which are not the result of an AE, need not be considered AEs and should be recorded on a clinical assessment form and added to the electronic case report form. If anything untoward is reported during the procedure, this must be reported as an AE and either 'serious' or 'nonserious' attributed according to the usual criteria.

Serious Adverse Event Reporting

Serious adverse events that occur between the time of signing the informed consent form and until 30 days after the last dose of study treatment, regardless of relationship to the study treatment, must be reported within 24 hours of knowledge of the event to the sponsor or designee. In addition, if the investigator learns at any time of an SAE which is believed to be related to the study treatment then this must be reported to the sponsor, even if more than 30 days have elapsed since the last dose of study treatment.

Serious adverse event reporting will be conducted as described in the safety management plan. The SAE form will collect all relevant data concerning the AE, including: details of the nature of the symptoms, time of onset, duration, and severity, together with an investigator's (or designee's) opinion of the relationship to study treatment, and any action taken in relation to the planned administration of study treatment. In addition, the investigator should provide relevant medical history, concomitant medications, laboratory or diagnostic test reports, details of any treatment for the SAE, and all other pertinent medical information.

Pregnancy

Pregnancy (maternal or paternal exposure to study treatment) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Appendix 2: Clinical Laboratory Evaluations

Clinical chemistry:	**Hematology:**	**Urinalysis:**
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Calcium Chloride Cholesterol Total High-density lipoprotein Low-density lipoprotein C-reactive protein Creatinine Direct bilirubin Gamma-glutamyl transferase Glucose Inorganic phosphate Potassium Sodium Total bilirubin Total CO_2 Total protein Uric acid	Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Absolute reticulocyte count Red blood cell count White blood cell (WBC) count WBC differential (absolute count): Basophils Eosinophils Lymphocytes Monocytes Neutrophils Large unclassified cells **Coagulation profile:** Activated partial thromboplastin time International normalized ratio Prothrombin time	Blood Glucose Ketones pH Protein Specific gravity Urobilinogen Microscopic examination
Serology:	**Drug screen:**	**Hormone panel - females only:**
Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency virus (HIV-1 and HIV-2) antibodies and p24 antigen Quantiferon™ tuberculosis Gold	Including but not limited to: Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates Tetrahydrocannabinol/ cannabinoids Tricyclic antidepressants Alcohol[c]	Follicle-stimulating hormone[a] Serum pregnancy test (human chorionic gonadotropin)[b] Urine pregnancy test[b]

[a] Performed for all females in serum at timepoints detailed in Appendix 6.
[b] Performed for all females in serum at timepoints detailed in Appendix 6. A positive urine pregnancy test will be confirmed with a serum pregnancy test.
[c] Alcohol breath test performed at timepoints detailed in Appendix 6.

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject in Part A (single ascending dose).

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Full clinical laboratory evaluations	9.3	4	37.2
Serology	3.5	1	3.5
Quantiferon™ TB Gold test	4	1	4
AQ280/AQ282 PK[a]	4	17	68
CCI PD[a,b]	2	8	16
CCI PD[a,b]	2.5	8	20
Total:			148.7

Abbreviations: PD = pharmacodynamics; PK = pharmacokinetics; TB = tuberculosis.
[a] Includes 3 potential additional samples.
[b] Additional assessments performed outside of full clinical laboratory evaluations.

The following blood volumes will be withdrawn for each subject in Part A (single ascending dose) for the food effect evaluation.

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Full clinical laboratory evaluations	9.3	7	65.1
Serology	3.5	1	3.5
Quantiferon™ TB Gold test	4	1	4
AQ280/AQ282 PK[a]	4	34	136
CCI PD[a,b]	2	8	16
CCI PD[a,b]	2.5	8	20
Total:			244.6

Abbreviations: PD = pharmacodynamics; PK = pharmacokinetics; TB = tuberculosis.
[a] Includes 3 potential additional samples per treatment period.
[b] Additional assessments performed outside of full clinical laboratory evaluations.

If extra blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed 550 mL.

The following blood volumes will be withdrawn for each subject in Part B (multiple ascending dose).

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Full clinical laboratory evaluations	9.3	7	65.1
Serology	3.5	1	3.5
Quantiferon™ TB Gold test	4	1	4
AQ280/AQ282 PK[a]	4	32	128
CCI [redacted] PD[a,b]	2	5	10
CCI [redacted] PD[a,b]	2.5	5	12.5
CCI [redacted] PD[a,b]	4	5	20
Total:			243.1

Abbreviations: CCI [redacted] PD = pharmacodynamics; PK = pharmacokinetics; TB = tuberculosis.
[a] Includes 3 potential additional samples.
[b] Additional assessments performed outside of full clinical laboratory evaluations.

If extra blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed 550 mL.

Appendix 4: Contraception Guidance

Definitions

Female of Childbearing Potential: premenopausal female who is anatomically and physiologically capable of becoming pregnant following menarche.

Female of Nonchildbearing Potential:

1. **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 a minimum of 6 weeks, or at the investigator's discretion, prior to screening.
2. **Postmenopausal:** female at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone (FSH) level of ≥40 mIU/mL. 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 such as 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. Females 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.

Contraception Guidance

Female Subjects

Female subjects who are of nonchildbearing potential will not be required to use contraception. For female subjects of childbearing potential, 2 methods (1 primary acceptable and 1 secondary method) of birth control are required from the time of signing the informed consent form (ICF) until 90 days after the follow-up phone call or visit. Primary (non-barrier) methods of contraception include:

- hormonal injection (as prescribed)
- combined oral contraceptive pill or progestin/progestogen-only pill (as prescribed)
- combined hormonal patch (as prescribed)
- combined hormonal vaginal ring (as prescribed)
- surgical method performed at least 3 months prior to the screening visit:
  - bilateral tubal ligation
  - Essure® (hysteroscopic bilateral tubal occlusion) with confirmation of occlusion of the fallopian tubes
- hormonal implant
- hormonal or non-hormonal intrauterine device

- vasectomized male partner (sterilization performed at least 90 days prior to the screening visit, with verbal confirmation of surgical success, and the sole partner for the female subject).

A secondary (barrier) method of contraception would include:

- condom with spermicide.

Female subjects of childbearing potential should refrain from donation of ova from check-in (Day -1) until 90 days after the follow-up phone call or visit.

Male Subjects

Male subjects in conjunction with partners of childbearing potential use the following contraceptive measure:

- condom and spermicide (even if subject has a history of vasectomy).

In addition, use a second method of acceptable contraception from check-in until 90 days after discharge. 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 second method of contraception for male subjects is vasectomy that has been performed at least 90 days prior to the screening visit, with verbal confirmation of surgical success.

For male subjects (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 the follow-up phone call or visit. Male subjects are required to refrain from donation of sperm from check-in until 90 days after the follow-up phone call or visit.

Sexual Abstinence and Same-sex Relationships

A subject who practices total abstinence is required to identify contraceptive methods he/she will use in the event of sexual activity. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply. If a subject who is in a same-sex relationship at the time of signing the ICF becomes engaged in a heterosexual relationship, they must agree to use contraception as described previously.

Appendix 5: Regulatory, Ethical, and Study Oversight Considerations

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 Council for International Organizations of Medical Sciences International Ethical Guidelines.
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, informed consent form (ICF), investigator's brochure, and other relevant documents must be submitted to an ethics committee (EC) by the investigator and reviewed and approved by the EC before the study is initiated.

Any substantial protocol amendments, likely to affect the safety of the subjects or the conduct of the study, will require EC and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects or any nonsubstantial changes, as defined by regulatory requirements.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the EC annually or more frequently in accordance with the requirements, policies, and procedures established by the EC.
- Notifying the EC of serious adverse events or other significant safety findings as required by EC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the EC, European Directive 2001/20/EC for clinical studies (if applicable), Clinical Trials Regulation (EU) 536/2014, and all other applicable local regulations.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

Prior to starting participation in the study, each subject will be provided with a study-specific ICF giving details of the study treatments, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the investigator (or designee) and that their participation is voluntary and they are free to withdraw from the study at any time. Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation.

Following discussion of the study with study site personnel, subjects will sign the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving their informed consent. A copy of the ICF will be given to the subject.

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

Subject Data Protection

Subjects will be assigned a unique identifier and will not be identified by name in electronic case report forms (eCRFs), study-related forms, study reports, or any related publications. Subject and investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual subjects or investigator will be redacted according to applicable laws and regulations.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her study-related data may be examined by sponsor or contract research organization (CRO) auditors or other authorized personnel appointed by the sponsor, by appropriate EC members, and by inspectors from regulatory authorities.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The investigator (or designee) agrees not to disclose such information in any way without prior written permission from the sponsor.

Data Quality Assurance

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly 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.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, EC review, and regulatory agency inspections and provide direct access to source data documents.
- Labcorp Drug Development is responsible for the data management of this study, including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a project management plan. Additional details of quality checking to be performed on the data may be included in a data management plan.

- A study monitor 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 subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator in the study site archive for at least 5 years after the end of the study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Investigator Documentation Responsibilities

All individual, subject-specific study data will also be entered into a 21 CFR Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to Labcorp Drug Development electronically, will be integrated with the subject's eCRF data in accordance with the data management plan.

An eCRF must be completed for each enrolled subject who undergoes any screening procedures, according to the eCRF completion instructions. The sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Publications

Publications will be addressed in a separate agreement.The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix 6: Schedule of Assessments

Schedule of Assessments – Part A (Single Ascending Dose)

Visit Name	**Screening**	**Check-in**	**Treatment period**			**Follow-up[a]**	**Early termination (if applicable)**	**Comment (*)**
Visit No.	**1**	**2**				**3**		
Day No. Visit window (calendar days)	**-35 to -2**	**-1**	**1**	**2**	**3**	**8** (±2 days)		
Trial population and eligibility								
Informed consent*	X							The ICF must be signed prior to performing any protocol-related procedures, including, but not limited to, screening evaluations.
Subject eligibility	X	X						
Demographics	X							
Medical history	X							
Height and weight	X							
Alcohol breath test	X	X						
Urine drug screen	X	X						
Serology*	X							Hep B surface antigen, hep C virus antibody, HIV antibodies.
Quantiferon™ TB Gold test	X							
Serum pregnancy test*	X							All females.
FSH*	X							All females.
Trial residency								
Check-in		X						
Check-out					X			
Nonresidential visit	X							
Treatment and randomization								
Concomitant medication and concurrent procedures	X	X	X	X	X	X	X	
Randomization			X					
IMP administration*			X					Subjects will be dosed in a fasted state.
Safety assessments								
Physical examination*		X			X		X	Full physical examination performed at check-in. Symptom-directed physical examination at all other times.

Visit Name	**Screening**	**Check-in**	**Treatment period**			**Follow-up[a]**	**Early termination (if applicable)**	**Comment (*)**
Visit No.	**1**	**2**				**3**		
Day No. Visit window (calendar days)	**-35 to -2**	**-1**	**1**	**2**	**3**	**8** (±2 days)		
Vital signs	X	X	X*	X*	X*		X	Day 1: Predose (triplicate), 1, 2, 4, 6, 8, and 12 hours postdose. Day 2: 24 hours postdose. Day 3: 48 hours postdose. Timepoints may be adjusted based on emerging data.
Safety ECG	X	X	X*	X*	X*		X	Day 1: Predose (triplicate), 2, 4, and 8 hours postdose. Day 2: 24 hours postdose. Day 3: 48 hours postdose.
Telemetry/continuous ECG*			X*	X*				See footnote b. Day 1: 3 readings predose (-60, -45, and -30 minutes), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours postdose. Day 2: 24 hours postdose.
All hematology, coagulation, and clinical chemistry	X	X		X*	X*		X	Day 2: 24 hours postdose. Day 3: 48 hours postdose.
Urinalysis	X	X			X*		X	Day 3: 48 hours postdose.
Urine pregnancy test*		X			X		X	Only female subjects.
Adverse events	X	X				X	X	
PK/PD assessments								
PK blood sample*			X*	X*	X*		X	See footnote c. Day 1: Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours postdose. Day 2: 24 and 36 hours postdose. Day 3: 48 hours postdose.
CCI [redacted]			X*	X*				Day 1: Predose, 1, 4, 8, and 12 hours postdose. Day 2: 24 hours postdose (analyzed as part of scheduled hematology and clinical chemistry evaluations).

Abbreviations: DEC = dose escalation committee; ECG = electrocardiogram; FSH = follicle-stimulating hormone; Hep = hepatitis; HIV = human immunodeficiency virus; ICF = informed consent form; IMP = investigational medicinal product; PD = pharmacodynamic; PK = pharmacokinetic; TB = tuberculosis.

[a] All subjects will have a final safety follow-up, conducted via a phone call, 1 week (±2 days) after the final dose.

[b] Monitor for 12-lead ECG recording will be worn from approximately 2 hours predose to approximately 25 hours postdose on Day 1.
[c] The DEC may decide to alter the sampling schedule, allowing for up to 3 additional samples to be taken and additional outpatient visits included if additional samples beyond 48 hours postdose are required. Such visits will not occur more than 7 days after the last dosing.

Schedule of Assessments – Part A (Food Effect Evaluation Group)

Visit Name	Screening	Period 1				Period 2[a]					Early termination (if applicable)	Comment (*)
		Check-in	Treatment period			Check-in	Treatment period			Follow-up[b]		
Visit No.	**1**	**2**				**3**				**4**		
Period Day No. Visit window (calendar days)	**-35 to -2**	**-1**	**1**	**2**	**3**	**-1**	**1**	**2**	**3**	**8** (±2 days)		
Trial population and eligibility												
Informed consent*	X											The ICF must be signed prior to performing any protocol-related procedures, including, but not limited to, screening evaluations.
Subject eligibility	X	X										
Demographics	X											
Medical history	X											
Height and weight	X											
Alcohol breath test	X	X				X						
Urine drug screen	X	X				X						
Serology*	X											Hep B surface antigen, hep C virus antibody, HIV antibodies.
Quantiferon™ TB Gold test	X											
Serum pregnancy test*	X											All females.
FSH*	X											All females.
Trial residency												
Check-in		X				X						
Check-out					X				X			
Nonresidential visit	X											
Treatment and randomization												
Concomitant medication and concurrent procedures	X	X	X	X	X	X	X	X	X	X	X	
Randomization			X									

Visit Name	Screening	Period 1				Period 2[a]					Early termination (if applicable)	Comment (*)
		Check-in	Treatment period			Check-in	Treatment period			Follow-up[b]		
Visit No.	**1**	**2**				**3**				**4**		
Period Day No. Visit window (calendar days)	**-35 to -2**	**-1**	**1**	**2**	**3**	**-1**	**1**	**2**	**3**	**8** (±2 days)		
IMP administration			X*				X*					Subjects in Period 1 will be dosed in a fasted state. Subjects in Period 2 will be dosed 30 minutes after a high-fat breakfast. 2 treatment periods separated by a washout of ≥7 days.
Safety assessments												
Physical examination*		X			X	X			X		X	Full physical examination performed at check-in for Period 1. Symptom-directed physical examination at all other times.
Vital signs	X	X	X*	X*	X*	X	X*	X*	X*		X	Day 1: Predose (triplicate), 1, 2, 4, 6, 8, and 12 hours postdose. Day 2: 24 hours postdose. Day 3: 48 hours postdose. Timepoints may be adjusted based on emerging data.
Safety ECG	X	X	X*	X*	X*	X	X*	X*	X*		X	Day 1: Predose (triplicate), 2, 4, and 8 hours postdose. Day 2: 24 hours postdose. Day 3: 48 hours postdose.
Telemetry/continuous ECG			X*	X*								See footnote c. Day 1: 3 readings predose (-60, -45, and -30 minutes), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours postdose. Day 2: 24 hours postdose.
All hematology, coagulation, and clinical chemistry	X	X		X*	X*	X		X*	X*		X	Day 2: 24 hours postdose. Day 3: 48 hours postdose.
Urinalysis	X	X			X*	X			X*		X	Day 3: 48 hours postdose.
Urine pregnancy test*		X			X	X			X		X	Only female subjects.
Adverse events	X	X				X				X	X	

Visit Name	Screening	Period 1				Period 2[a]					Early termination (if applicable)	Comment (*)
		Check-in	Treatment period			Check-in	Treatment period			Follow-up[b]		
Visit No.	**1**	**2**				**3**				**4**		
Period Day No. Visit window (calendar days)	**-35 to -2**	**-1**	**1**	**2**	**3**	**-1**	**1**	**2**	**3**	**8** (±2 days)		
PK/PD assessments												
PK blood sample*			X*	X*	X*		X*	X*	X*		X	See footnote d. Day 1: Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours postdose. Day 2: 24 and 36 hours postdose. Day 3: 48 hours postdose.
CCI [redacted]			X*	X*								Period 1 only. Day 1: Predose, 1, 4, 8, and 12 hours postdose. Day 2: 24 hours postdose (analyzed as part of scheduled hematology and clinical chemistry evaluations).

Abbreviations: DEC = dose escalation committee; ECG = electrocardiogram; FSH = follicle-stimulating hormone; Hep = hepatitis; HIV = human immunodeficiency virus; ICF = informed consent form; IMP = investigational medicinal product; PD = pharmacodynamic; PK = pharmacokinetic; TB = tuberculosis.

Note: If conduct of Period 2 is delayed, a safety follow-up phone call may be done 1 week (±2 days) after dosing in Period 1.

[a] Subjects participating in the food effect evaluation group will have 2 treatment periods separated by a washout of ≥7 days. Sponsor will decide if the food interaction should be conducted based on emerging data.

[b] All subjects will have a final safety follow-up, conducted via a phone call, 1 week (±2 days) after the final dose.

[c] Monitor for 12-lead ECG recording will be worn from approximately 2 hours predose to approximately 25 hours postdose on Day 1 in Period 1 only.

[d] The DEC may decide to alter the sampling schedule, allowing for up to 3 additional samples to be taken and additional outpatient visits included if additional samples beyond 48 hours postdose are required. Such visits will not occur more than 7 days after the last dosing.

Schedule of Assessments – Part B (Multiple Ascending Dose)

Visit Name	**Screening**	**Check- in**	**Treatment period**									**Follow-up**	**Early Termination (if applicable)**	**Comment (*)**
Visit No.	**1**	**2**										**3**		
Day No. Visit window (calendar days)	**-35 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**14** ±3 days		
Trial population and eligibility														
Informed consent*	X													The ICF must be signed prior to performing any protocol-related procedures, including, but not limited to, screening evaluations.
Subject eligibility	X	X												
Demographics	X													
Medical history	X													
Height	X													
Alcohol breath test	X	X												
Urine drug screen	X	X												
Serology*	X													Hep B surface antigen, hep C virus antibody, HIV antibodies
Quantiferon™ TB Gold test	X													
Serum pregnancy test*	X													All females.
FSH*	X													All females.
Trial residency														
Check-in		X												
Check-out											X			
Nonresidential visit	X											X		

Visit Name	Screening	Check- in	Treatment period									Follow-up	Early Termination (if applicable)	Comment (*)
Visit No.	**1**	**2**										**3**		
Day No. Visit window (calendar days)	**-35 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**14** ±3 days		
Treatment and randomization														
Concomitant medication and concurrent procedures	X	X	X									X	X	
Randomization			X											
IMP administration*			X	X	X	X	X	X	X					QD, approximately same time each morning.
Safety assessments														
Vital signs	X	X	X*	X*	X*	X*	X*	X*	X*	X*	X*	X	X	Timepoints may be adjusted based on emerging data. Day 1: Predose (triplicate), 2, 4, and 8 hours postdose. Days 2 to 6: Predose and t_{max}[a]. Day 7: Predose, 2, 4, and 8 hours post Day 7 dose. Day 8: 24 hours post Day 7 dose. Day 9: 48 hours post Day 7 dose.
Physical examination*		X									X	X	X	Full physical examination at check-in. Symptom-directed physical examination at all other times.
Weight	X	X									X	X	X	
Safety ECG	X	X	X*		X*		X*		X*	X*	X*	X	X	Day 1: Predose (triplicate), t_{max}[a]. Days 3 and 5: Predose. Day 7: Predose, t_{max}[a]. Day 8: 24 hours post Day 7 dose. Day 9: 48 hours post Day 7 dose.

Visit Name	Screening	Check- in	Treatment period									Follow-up	Early Termination (if applicable)	Comment (*)
Visit No.	1	2										3		
Day No. Visit window (calendar days)	-35 to -2	-1	1	2	3	4	5	6	7	8	9	14 ±3 days		
All hematology, coagulation, and clinical chemistry	X	X		X*		X*			X*		X*	X	X	Day 2: 24 hours postdose (collected prior to dose on Day 2). Days 4 and 7: Predose. Day 9: 48 hours post Day 7 dose.
Urinalysis	X		X*			X*			X*		X*	X	X	Days 1, 4, and 7: Predose. Day 9: 48 hours post Day 7 dose.
Urine pregnancy test*		X										X	X	Only female subjects.
Adverse events	X	X										X	X	
PK/PD assessments														
PK blood sample*			X*	X*	X*	X*	X*	X*	X*	X*	X*		X	See footnote b. Day 1: Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours postdose. Day 2: 24 hours postdose. Days 3 through 6: Predose. Day 7: Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours postdose. Day 8: 24 hours post Day 7 dose. Day 9: 48 hours post Day 7 dose.
CCI [redacted]			X*						X*	X*	X*			See footnote c. Day 1: Predose (spot collection), 0-8, 8-16, and 16-24 hours postdose. Day 7: 0-8, 8-16, and 16-24 hours postdose. Day 8: 24-36 hours post Day 7 dose. Day 9: 36-48 hours post Day 7 dose.

Visit Name	Screening	Check- in	Treatment period									Follow-up	Early Termination (if applicable)	Comment (*)
Visit No.	1	2										3		
Day No. Visit window (calendar days)	-35 to -2	-1	1	2	3	4	5	6	7	8	9	14 ±3 days		
CCI			X*			X*			X*	X*	X*			Day 1: Predose. Day 4: Predose (analyzed as part of scheduled hematology and clinical chemistry evaluations). Day 7: Predose (analyzed as part of scheduled hematology and clinical chemistry evaluations). Day 8: 24 hours post Day 7 dose. Day 9: 48 hours post Day 7 dose (analyzed as part of scheduled hematology and clinical chemistry evaluations).
CCI			X*			X*			X*	X*	X*			Days 1, 4, and 7: Predose. Day 8: 24 hours post Day 7 dose. Day 9: 48 hours post Day 7 dose.

Abbreviations: CCI DEC = dose escalation committee; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; Hep = hepatitis; HIV = human immunodeficiency virus; CCI ; ICF = informed consent form; IMP = investigational medicinal product; CCI MAD = multiple ascending dose; PD = pharmacodynamic; PK = pharmacokinetic; QD = once daily; TB = tuberculosis; t_{max} = time of the maximum observed concentration.

[a] Timepoint will coincide with t_{max} established in Part A.

[b] The DEC may decide to alter the sampling schedule, allowing for up to 3 additional samples to be taken and additional outpatient visits included if additional samples beyond 48 hours postdose are required. Such visits will not occur more than 7 days after the last dosing.

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