# STUDY PROTOCOL

| | |
|---|---|
| **STUDY TITLE:** | A Randomised, Double-blind, Placebo-controlled, Study of the Safety, Tolerability, and Pharmacokinetics of AX-158 Following Administration of Single and, Multiple Ascending Oral Doses and Food Effect sub-study in Healthy Male Volunteers. |
| **STUDY NUMBER:** | RD 675/34625<br>AX-158-101 |
| **EudraCT NUMBER:** | 2021-002541-16 |
| **IRAS ID:** | 295109 |
| **INVESTIGATIONAL MEDICINAL PRODUCT(s):** | • AX-158 5 mg Capsule<br>• Placebo Capsule |
| **PLANNED STUDY DOSES:** | Part A - Single Ascending Dose (SAD)<br>Part B - Food Effect<br>Part C - Multiple Ascending Dose (MAD) |
| **PRINCIPAL INVESTIGATOR:** | Dr Annelize Koch<br>Simbec-Orion<br>Merthyr Tydfil<br>CF48 4DR, UK |
| **STUDY SPONSOR:** | Artax Biopharma Inc |
| **SPONSOR'S RESPONSIBLE PHYSICIAN:** | Dr Richard Polisson<br>Artax Biopharma, Inc<br>One Broadway<br>14th Floor<br>Cambridge, MA 02142 |
| **STUDY MONITOR:** | Simbec-Orion Clinical Development |

| | |
|---|---|
| **SPONSOR LEGAL REPRESENTIVE:** | Orion LR<br>Merthyr Tydfil Industrial Park, Pentrebach,<br>Merthyr Tydfil,<br>CF48 4DR, UK. |
| **ADDITIONAL DEPARTMENTS:** | Simbec-Orion Laboratory Services<br>Merthyr Tydfil Industrial Park, Pentrebach,<br>Merthyr Tydfil,<br>CF48 4DR, UK. |

## PROTOCOL FINALISATION STATEMENT

This protocol is not considered final unless accompanied by an approval letter from the Research Ethics Committee and Notice of Acceptance from the relevant Competent Authority.

**Protocol Prepared by: AC**

# 1 SIGNATURE PAGE

I declare that I have read and understood this study protocol. I agree to abide by this protocol (subject to any amendments agreed in writing between the Sponsor and Principal Investigator). Any changes in procedure will only be made if necessary, to protect the safety, rights, or welfare of the participants.

**STUDY SPONSOR:**

Richard Polisson, M.D
Artax Biopharma, Inc
One Broadway
14th Floor
Cambridge, MA 02142

☎ 617-368-0676

email rpolisson@artaxbiopharma.com

Signature: DocuSigned by: Richard Polisson
Signer Name: Richard Polisson
Signing Reason: I approve this document
Signing Time: 14-Jan-2022 | 14:28 PST
5D68449A7A484F37B1A3BF32A012FA7E

Date:

**PRINCIPAL INVESTIGATOR:**

Dr Annelize Koch
Simbec-Orion
Merthyr Tydfil CF48 4DR
UK

☎ +44 (0)1443 690977

email annelize.koch@simbecorion.com

Signature: DocuSigned by: Annelize Koch
Signer Name: Annelize Koch
Signing Reason: I approve this document
Signing Time: 15-Jan-2022 | 08:10 GMT
9B632C24B4B34F7E8F514510788D4968

Date:

# 2 PROTOCOL AMENDMENT/REVISION HISTORY

| Protocol Version/ Date | Type of Amendment | Amendment Rationale | Sections Affected | Summary of Amendment / Changes to the Protocol |
|---|---|---|---|---|
| V1.0 26 May 2021 | N/A | N/A | N/A | N/A – Initial Version |
| V2.0, 22 June 2021 | N/A | Response to MHRA Grounds for Non-Acceptance | Section 8.5 – Toxicology | - Section updated to include reference to pre-defined exposure limits for $C_{max}$ & $AUC_{0-24}$ as per MHRA request. |
| | | | Section 10.3.4 - Progression from Dose Leader Group/Dose Escalation Stopping Criteria | - Stopping criteria for systemic exposure updated to include reference to pre-defined exposure limits for $C_{max}$ & $AUC_{0-24}$ as per MHRA request. |
| | | | Section 10.8.7 – Selection of Doses in the Study | - Additional text included as per MHRA request to clarify planned study doses in the context of the estimated human pharmacodynamic range. |
| V3.0, 22 October 2021 | Non-Substantial | To align with latest version of Simbec-Orion protocol template | Section 3 – Synopsis | - Changes implemented to align with main body text |
| | | | Section 5 – Abbreviations | - Abbreviations' list updated to include additional abbreviations to align with latest version of Simbec-Orion template |
| | | | Section 8.2 – Physical, Chemical and | - Capsule size updated from size 3 to size 2 |

| | | | | |
|---|---|---|---|---|
| | | | Pharmaceutical Properties and Formulation | |
| | | | Section 8.8 - Coronavirus Disease 2019 (COVID-19) Risk/Benefit Assessment | - Full definition of NHS, PPE & IMP added |
| | | | Section 10.3.1 – Dose Escalation Procedures | - Removal of term ‘accrual’ in relation to dose escalation for review of PK and safety data.<br><br>- Removal of term ‘pharmacist’ and replaced with ‘IMP Management team’<br><br>- Addition of text to confirm that receipt of the signed dose escalation approval form will trigger the release of the IMP for the next dose level to the clinic. |
| | | | Section 10.5 – Selection of Study Population | - Full definition of SI added |
| | | | Section 10.5.1 – Inclusion Criteria | - Criterion #11 updated to include full definition of QTcF<br><br>- Criterion #12 updated to replace ‘pulse’ with ‘heart rate’ as per latest version of Simbec-Orion protocol template |

| | | | | |
|---|---|---|---|---|
| | | | | – Criterion #16 updated to include full definition for RT-PCR |
| | | | Section 10.6.1 – Contraception | - Statement added to vasectomised partner contraception method to note that if there is no documentation to support the absence of sperm in the ejaculate, then condoms will still be required for these individuals. |
| | | | Section 10.8.2 – Receipt and Storage & Section 10.8.3 – Assembly and Release | - Full definition of API added.<br><br>- Revision of term 'The Pharmacy' to 'IMP Management'<br><br>- Removal of reference to specific Simbec-Orion SOP numbers and replaced with 'Simbec-Orion SOPs.'<br><br>- Revision of storage conditions for IMP from quarantine in a segregated, study specific area within the pharmacy to quarantine within a GMP area to facilitate circumstances where IMP may be stored within the clinical unit or other areas as needed. |
| | | | Section 10.8.11 - Blinding | - Revision of term 'pharmacist' to 'IMP |

| | | | | |
|---|---|---|---|---|
| | | | | Management' or 'team' where relevant. |
| | | | Table 10.9.1 – Study Flow Chart – Part A Single Ascending Dose | - Footnote #8 updated to replace 'pulse' with 'heart rate' as per latest version of Simbec-Orion protocol template |
| | | | Table 10.9.2 – Study Flow Chart – Part B Food Effect | - Footnote #8 updated to replace 'pulse' with 'heart rate' as per latest version of Simbec-Orion protocol template |
| | | | Table 10.9.3 – Study Flow Chart – Part C Multiple Ascending Dose | - Footnote #9 updated to replace 'pulse' with 'heart rate' as per latest version of Simbec-Orion protocol template |
| | | | Section 10.9.2.4 - COVID-19 PCR Testing | – Full definition of RT-PCR removed |
| | | | Section 10.9.2.5 - Drug of Abuse and Alcohol | – Full definition of DOA removed |
| | | | Section 10.9.5.1 – Adverse Events | – Full definition of SI removed |
| | | | Section 10.9.5.1.1.1 – Recording of Adverse Events | – Full definition of SAE removed |
| | | | Section 10.9.7 - Other Safety Assessments & Section 10.11.2 – Study Variables/ Endpoints & | – Vital signs parameters updated to replace 'pulse' with 'heart rate' as per latest version of Simbec-Orion protocol template |

| | | | | |
|---|---|---|---|---|
| | | | Appendix 1 – Normal Ranges for Vital Signs and ECG Parameters | |
| V4.0 14/January 2022 | Substantial | Updates to study design | Protocol Section 3 – Synopsis | |
| | | | Protocol Section 5 – Abbreviations | |
| | | | Protocol Section 8.8 - Coronavirus Disease 2019 (COVID-19) Risk/Benefit Assessment | Risk/benefit assessment updated to reflect the requirement for all participants enrolled into the study to be fully vaccinated against COVID-19 as per the current Welsh/UK Government guidelines |
| | | | Protocol Section 10.2 – Adaptive Elements | Adaptive design elements updated to indicate that the timing of exploratory PD samples in both Part A and Part C. |
| | | | Protocol Section 10.5.1 – Inclusion Criteria | Criterion #16 updated<br>New criterion #17 |
| | | | Table 10.9.1, 10.9.2, 10.3.3 – Study Flow Charts | Flow chart updated to include timepoints for exploratory PD sampling<br>Part C flow updated to capture additional COVID-19 tests |
| | | | Protocol Section 10.9.6 – COVID-19 Testing | Section updated to reference routine performance of Lateral Flow Testing |

| | | | | |
|---|---|---|---|---|
| | | | Table 10.9.4, 10.9.6 Summary of Blood Volumes | Blood volume updated to reflect addition of exploratory PD samples |
| | | | Protocol Section 10.9.26 – Other Assessments | New section added to describe the procedures for collection of exploratory PD samples |
| | | | Protocol Section 10.10.1 - Summary of Source Documentation Location | Addition of reference to PD sample collection |
| | | | Protocol Section 10.11.2 – Study Variables/Endpoints | Endpoints for derived plasma PK for all study parts updated to include AUC0-24 |
| | | | Protocol Section 10.11.8 – PK Data | Text updated to include AUC0-24 |

# 3 SYNOPSIS

| |
|---|
| **NAME OF COMPANY:** Artax Biopharma Inc |
| **NAME OF INVESTIGATIONAL MEDICINAL PRODUCT:** AX-158, Placebo |
| **NAME OF ACTIVE INGREDIENT:** AX-158 |
| **TITLE OF STUDY**: A Randomised, Double-blind, Placebo-controlled, Study of the Safety, Tolerability, and Pharmacokinetics of AX-158 Following Administration of Single and, Multiple Ascending Oral Doses and Food Effect sub-study in Healthy Male Volunteers. |
| **PRINCIPAL INVESTIGATOR:** Dr Annelize Koch |
| **STUDY CENTRE:** Simbec-Orion Clinical Pharmacology<br>Merthyr Tydfil, CF48 4DR, UK |
| **CLINICAL PHASE:** I |
| **OBJECTIVES:**<br>Primary Objective<br>• To assess the safety and tolerability of single and multiple ascending doses of AX-158 when administered to healthy participants (Part A and Part C).<br>Secondary Objective<br>• To investigate the PK of single and multiple doses of AX-158 in healthy participants (Part A and Part C).<br>• To investigate any food effect on the PK of AX-158 following oral administration of a single dose to healthy participants (Part B). |
| **METHODOLOGY:**<br>This is a phase I, randomised, double-blind, placebo-controlled study to investigate the safety, tolerability, and PK of AX-158 in healthy male participants following single (Part A) and multiple (Part C) ascending doses including food effect (Part B).<br><br>The study will be conducted in three parts (Part A, Part B and Part C).<br><br>Part A (SAD) will enrol 8 participants per cohort randomised (3:1) to receive AX-158 (6 participants) or placebo (2 participants). Part A will follow a single ascending dose (SAD) design with all participants receiving one dose of AX-158 (or placebo) in the fasted state.<br><br>Part B (Food Effect) will be conducted in 8 participants in a cross-over manner; each participant will receive AX-158 in the fed and fasted state.<br><br>Part C (MAD) will enrol 8 participants pre cohort randomised to (3:1) to receive AX-158 (6 participants) or placebo (2 participants). Part C will follow a multiple ascending dose (MAD) design with participants receiving AX-158 (or placebo) once daily for 10 consecutive days, in a fed or fasted state (depending on the outcome of the Part B (Food Effect). Doses, dosing duration and dose regimen (i.e., q.i.d., b.i.d., t.i.d.) of AX-158 and matching placebo for Part C may be modified based on all available safety, tolerability, and PK data and applied to additional MAD cohorts. Each participant will participate in only one cohort and in one of the study parts.<br><br>Part A (SAD) will be conducted in up to forty (40) participants (5 cohorts of 8 participants). An additional two cohorts of eight (8) participants each (up to 16 additional participants total) may be investigated if required. Part B (Food Effect) will be conducted in 8 participants in a cross-over manner. Part C (MAD) will be conducted in up to twenty-four (24) participants (3 cohorts of 8 participants). An additional two cohorts of eight (8) |

participants each (up to 16 additional participants total) may be investigated if required. Each participant will be assigned to only one study part and within each part, assigned to one cohort.

Participants in Part A (SAD) will undergo a screening period (Day -28 to Day -2), an in-house treatment period comprising 4 overnight stays (from Day -1 to Day 4) and a follow up visit 5-7 days following administration of AX-158 or placebo.

Participants in Part B (Food Effect) will undergo a screening period (Day -28 to Day -2), two in-house treatment periods comprising of 4 overnight stays (from Day -1 to Day 4) separated by a minimum of 7 days between doses and a follow up visit 5-7 days following the final administration of AX-158.

Participants in Part C (MAD) will undergo a screening period (Day -28 to Day -2), an in-house treatment period comprising 13 overnight stays (from Day -1 to Day 13) and a follow up visit 5-7 days following the final administration of AX-158 or placebo.

This study is designed to be adaptive, and the following elements may be revised based on emerging clinical safety and PK data during the course of the trial without a substantial amendment:

- Following review of the Part B Food effect cohort PK data, participants in Part C cohorts may be administered AX-158 under fasted or fed conditions, as deemed appropriate, pending DERC determination of any appreciable impact of food effect of AX-158. If food effect is seen, cohorts in Part C could be dosed with a standardised meal (as opposed to the high-fat breakfast). This decision will be documented in the Food Effect Cohort Dose Escalation Review meeting minutes.
- The timing, type, and number of safety, PK assessments may be modified (without extending the duration of the study).
- A minimum washout of 7 days is expected within Part B but may be extended based on emerging safety and PK data to 14 days.
- The number and/or volume of blood samples per assessment may be increased as long as the total volume of blood drawn for a participant does not exceed 10% of the pre-specified total blood volume or surpass 500 mL (except when extra blood samples need to be taken for safety reasons).
- In Part C (MAD), it is planned to dose AX-158 or placebo once daily for at least 10 consecutive days; doses dosing duration and dose regimen (i.e., q.i.d., b.i.d, t.i.d) of AX-158 and matching placebo for Part C may be modified based on all available safety, tolerability, and PK data and applied to additional MAD cohorts up to a maximum of 14 days.
- Dose levels/dosing regimen may be adjusted lower based on emerging safety and PK data.
- Additional dose level(s) may be examined if deemed safe and appropriate. These cohorts will enrol 8 participants (for SAD cohorts) and up to 8 participants (for MAD cohorts).
- Currently it is planned that in order to dose escalate between cohorts and between study parts, PK data from up to the 24 hr post-last time point in all parts and 72 hr post-last dose safety data is required. However, if during the course of dose escalation, it is determined necessary to do so, then dose escalation procedures may be extended in order to include additional PK data up to the 72 hr post-last dose time point in all study parts.
- Exploratory PD samples will be taken pre-dose in Part A (SAD) and Part C (MAD) additional sample(s) will be taken based on emerging data. The total blood volume will not exceed 500mL.

The clinical phase is anticipated to take place between Q3 2021 (first participant first visit) and Q2 2022. The conclusion of the study is defined as last participant last visit (in Part C). The study will take place in the Clinical Unit of Simbec-Orion Clinical Pharmacology under full medical and nursing supervision.

A schedule of all study assessments is provided in Table 10.9.1 (Part A SAD), Table 10.9.2 (Part B Food Effect) and Table 10.9.3 (Part C MAD).

**NUMBER OF PARTICIPANTS:**

Up to 104 healthy male participants may be enrolled into the study.

- Part A: 40 participants (5 cohorts of 8 participants each). An additional 2 cohorts of 8 participants each may be investigated if required (max. 16 additional participants).
- Part B: 8 participants (1 cohort of 8 participants).
- Part C: 24 participants (3 cohorts of 8 participants each). An additional 2 cohorts of 8 participants each may be investigated if required (max. 16 additional participants).

**MAIN INCLUSION CRITERIA:**

1. Healthy Male participant, between 18 and 50 years of age, inclusive.
2. Male participant (and partner of childbearing potential) willing to use a highly effective method of contraception in addition to a condom, if applicable (unless anatomically sterile or where abstaining from sexual intercourse is in line with the preferred and usual lifestyle of the participant) from first dose until 4 months after last dose of IMP.
3. Participant with a body mass index (BMI) of 18-30kg/$m^2$. BMI = body weight (kg) / [height (m)]$^2$.
4. No clinically significant history of previous allergy / sensitivity to AX-158 or any of the excipients contained within the IMP.
5. Participant with no history of autoimmune disease, cardiac disease, kidney disease or any food intolerance.
6. No clinically significant abnormal test results for serum biochemistry, haematology and/or urine analyses within 28 days before the first dose administration of the IMP.
7. Total serum bilirubin, alkaline phosphatase (ALP), aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 1.5 x upper limit of normal (ULN). If total bilirubin is above the upper limit of normal and is then fractionated, direct bilirubin must be within normal limits.
8. Total serum Testosterone levels 2 x above the lower limit of the normal range within 28 days before the first dose administration of the IMP.
9. Participant with a negative urinary drugs of abuse (DOA) screen (including alcohol) test results, determined within 28 days before the first dose administration of the IMP (N.B.: A positive test result may be repeated at the Investigator's discretion).
10. Participant with negative human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg)) and hepatitis C virus antibody (HCV Ab) test results at Screening.
11. No clinically significant abnormalities in 12-lead electrocardiogram (ECG) determined within 28 days before first dose of IMP including a QRS > 120ms, PR interval > 220ms and QT interval corrected using Fredericia's formula (QTcF) > 450ms.
12. No clinically significant abnormalities in vital signs (e.g., blood pressure/heart rate, respiration rate and oral temperature) determined within 28 days before first dose of IMP.
13. Participant must be available to complete the study (including all follow-up visits).
14. Participant must satisfy an Investigator about his fitness to participate in the study.
15. Participant must provide written informed consent to participate in the study.
16. Participants with a negative COVID-19 test on admission.
17. Participants who are considered fully vaccinated to COVID-19 as per the current Welsh/UK Government guidelines.

**MAIN EXCLUSION CRITERIA:**

1. A clinically significant history of gastrointestinal disorder likely to influence IMP absorption.

2. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 28 days or 5 half-lives (whichever is longer) prior to the first dose of IMP. Occasional use of paracetamol will be allowed.
3. Evidence of renal, hepatic, central nervous system, respiratory, cardiovascular, or metabolic dysfunction.
4. A clinically significant history of drug or alcohol abuse (defined as the consumption of more than 14 units [for male and female participants] of alcohol a week) within the past two years.
5. Inability to communicate well with the Investigators (i.e., language problem, poor mental development, or impaired cerebral function).
6. Participation in a New Chemical Entity (NCE) clinical study within the previous 3 months or five half-lives, whichever is longer, or a marketed drug clinical study within the 30 days or five half-lives, whichever is longer, before the first dose of IMP. *(Washout period between studies is defined as the period of time elapsed between the last dose of the previous study and the first dose of the next study).*
7. Donation of 450 mL or more blood within the 3 months before the first dose of IMP.
8. Vegans, vegetarians, or other dietary restrictions (e.g., restrictions for medical, religious, or cultural reasons, etc), which would prevent participants from consuming a high-fat breakfast or standardised meal.
9. Users of nicotine products i.e., current smokers or ex-smokers who have smoked within the 6 months prior to screening or users of cigarette replacements (i.e., e-cigarettes, nicotine patches or gums).
10. Participants who have received a COVID-19 vaccine injection within 28 days prior to the first dose of IMP.

**IMP ADMINISTRATION:**

**Part A**

The following IMPs will be administered:

- AX-158 capsules
- Matching placebo

The IMPs will be administered fasted (after an overnight fast of at least 10 h) with 240 mL water. More water may be provided (except PK days) if needed and the actual water taken with dose administration will be recorded in the eCRF.

**Part B**

Each participant will receive the following IMP over 2 treatment periods (1/period) in accordance with the randomisation code:

- AX-158 capsules

The IMP will be administered in either the fed or fasted (after an overnight fast of at least 10h or following consumption of a high-fat breakfast) state in accordance with the randomisation with 240 mL of water. More water may be provided (except PK days) if needed and the actual water taken with dose administration will be recorded in the eCRF.

**Part C**

The following IMPs will be administered:

- AX-158 capsules
- Matching placebo

The IMPs will be administered fasted (after an overnight fast of at least 10 h) with 240 mL water. More water may be provided (except PK days) if needed and the actual water taken with dose administration will be recorded in the eCRF. Participants must remain sitting for at least 1 h after dose. If food effect is observed, cohorts in Part C could be dosed with a standardised meal (as opposed to the high-fat breakfast).

**STUDY VARIABLES/ENDPOINTS:**

**PK**

**Part A**

The following plasma PK endpoints will be derived: $C_{max}$, $T_{max}$, $\lambda z$, $t_{1/2}$, $AUC_{0-24}$, $AUC_{0-t}$, $AUC_{0-inf}$, $AUC_{\%extrapolated}$, CL/F, Vz/F.

**Part B**

The following plasma PK endpoints will be derived: $C_{max}$, $T_{max}$, $T_{lag}$, $\lambda z$, $t_{1/2}$, $AUC_{0-24}$, $AUC_{0-t}$, $AUC_{0-inf}$, $AUC_{\%extrapolated}$, CL/F, Vz/F.

**Part C**

The following plasma PK endpoints will be derived on Day 1: $C_{max}$, $T_{max}$ and $AUC_{0-24}$, ($AUC_{0-\tau}$ will also be derived if dosing interval other than q.d.).

The following plasma PK endpoints will be derived on Final Dosing Day: $C_{max}$, $T_{max}$, $\lambda z$, $t_{1/2}$, $AUC_{0-24}$, ($AUC_{0-\tau}$ will also be derived if dosing interval other than q.d), $AUC_{0-t}$, $AUC_{0-inf}$, $AUC_{\%extrapolated}$, CL/F and Vz/F.

The following urine PK parameters will be derived on Day 1 and Final Dosing Day: Ae, Ae%, $CL_R$.

*Steady-State:* For each dose level, log-transformed trough concentration levels at pre-dose day 5 will be subjected to a mixed effects analysis of variance (ANOVA) with study day as a fixed effect and participant as a random effect in order to establish whether and when steady-state has been attained for each dose level. Back-transformed ratios for the comparisons of each consecutive day (i.e., Day 3/Day 2) will be presented along with corresponding 90 % CI.

*Accumulation:* For each dose level, log-transformed $C_{max}$ and $AUC_{0-\tau}$ values on Day 1 and Final Dosing Day (Day 10) will be subjected to an ANOVA with study day as a fixed effect and participant as a random effect. For comparison, point estimates and 90 % CI for the difference between Final Dosing Day (Day 10) and Day 1 will be constructed using the residual mean square error obtained from the ANOVA for each dose level. The point and interval estimates will then be back transformed to give estimates of the ratios of the geometric least squares means and corresponding 90 % CI.

**Safety Part A, B and C**

- AEs.
- Laboratory safety (biochemistry, haematology, coagulation, and urinalysis).
- Vital signs (systolic/diastolic blood pressure, heart rate, oral body temperature and respiratory rate).
- 12-lead ECG (Heart rate, PR interval, QRS width, RR interval, QT interval and QT interval corrected using Fredericia's formula (QTcF).

**STATISTICAL METHODS:**

There will be no formal hypothesis testing. All descriptive statistical analyses will be performed using the most recently released and available SAS® statistical software, unless otherwise noted. Continuous variables will be summarised by descriptive statistics (sample size [n], mean, standard deviation [SD], median, minimum, and maximum). Categorical variables will be summarised in frequency tables (n, frequencies, and percentages). Individual participant data will be presented in listings. Missing data will not be imputed unless otherwise stated. There will be a detailed description of participant disposition; participant demographics and baseline

| | |
|---|---|
| characteristics will be summarised. PK data will be presented descriptively and graphically. A review of safety data and available preliminary PK data will be conducted by the DERC. A statistical analysis plan (SAP) will fully describe the planned analyses for this study. | |
| **DURATION OF STUDY:** | Part A: approximately 6 weeks for each individual (from the screening to post-study follow-up).<br>Part B: approximately 8 weeks for each individual (from the screening to post-study follow-up).<br>Part C: approximately 7 weeks for each individual (from the screening to post-study follow-up). |

# 4 TABLE OF CONTENTS

## TABLES

# 5 ABBREVIATIONS USED IN THE PROTOCOL TEXT

- ABPI — Association of the British Pharmaceutical Industry
- ADME — absorption, distribution, metabolism, and excretion
- AE(s) — adverse event(s)
- Ae — amount and cumulative amount of dose excreted in urine over each collection interval
- Ae% — % and cumulative % of dose excreted in urine over each collection interval
- ALP — alkaline phosphatase
- ALT — alanine transaminase
- ANOVA — analysis of variance
- API — active pharmaceutical ingredient
- aPTT — activated partial thromboplastin time
- AST — aspartate transaminase
- AUC — area under the concentration versus time curve
- $AUC_{0-24}$ — AUC from time zero to time 24 h postdose
- $AUC_{0-inf}$ — AUC extrapolated to infinity from dosing time, based on the last measurable concentration
- $AUC_{0-t}$ — AUC from the time of dosing to the time of the last measurable concentration
- $AUC_{0-\tau}$ — AUC from 0 to τ, where τ is the dosing interval.
- $AUC_{\%extrapolated}$ — residual area
- BIA — BioIndustry Association
- BMI — body mass index
- bpm — beat(s) per minute
- $C_{max}$ — maximum plasma concentration
- Ca — calcium
- CCRA — Clinical Contract Research Association
- CI — confidence interval
- CK — creatine kinase
- Cl — chloride
- CL/F — clearance
- $CL_R$ — renal clearance
- cm — centimetres
- CNS — central nervous system
- COVID-19 — coronavirus disease 2019
- CRF — case report form
- CRP — c-reactive protein
- CV% — coefficient of variation
- CYP — Cytochrome
- DERC — Dose Escalation Review Committee
- DMP — Data Management Plan
- DOA — drugs of abuse
- DoH — Department of Health
- EAE — Experimental autoimmune encephalomyelitis
- EC — European Commission
- eCRF — electronic case report form
- ECG — electrocardiogram
- EDTA — ethylenediaminetetraacetic acid
- EMA — European Medicine Agency
- EU — European Union
- FIH — First in Human
- g — gramme(s)
- GCP — Good Clinical Practice
- GDPR — General Data Protection Regulation
- GGT — gamma glutamyltransferase
- GLP — Good Laboratory Practice
- GMP — Good Manufacturing Practice
- h — hour(s)
- Hb — haemoglobin
- HBsAg — hepatitis B surface antigen
- HCV Ab — hepatitis C virus antibody
- $HCO_3$ — bicarbonate
- HED — human equivalent dose

- HIV human immunodeficiency virus
- HRA Health Research Authority
- IB Investigator's Brochure
- ICF informed consent form
- ICH International Council on Harmonisation
- IMP investigational medicinal product(s)
- INR international normalised ratio
- ISF Investigator site file
- IUD intrauterine device(s)
- IUS intrauterine system
- K potassium
- $k_{el}$ elimination rate constant
- LC MS/MS liquid chromatography tandem mass spectrometry
- LFT lateral flow test
- LH luteinising hormone
- LLOQ lower limit of quantification
- Ltd Limited
- MAD Multiple Ascending dose
- MCH mean corpuscular haemoglobin
- MCHC mean corpuscular haemoglobin concentration
- MCV mean corpuscular volume
- MedDRA Medical Dictionary for Regulatory Activities
- m metre(s)
- MHRA Medicines and Healthcare products Regulatory Agency
- mg milligram(s)
- mL millilitre(s)
- min minute
- mmHg millimetre(s) of mercury
- ms millisecond(s)
- MRSD maximum recommended starting dose
- MTD maximum tolerated dose
- N number dosed
- n number of observations
- Na sodium
- NCE new chemical entity
- NHS National Health Service
- NOAEL no-observed-adverse-effect level
- NRES National Research Ethics Committee
- PBMC peripheral blood mononuclear cell
- PCH Prince Charles Hospital
- PCE polychromatic erythrocytes
- PD pharmacodynamic
- PK pharmacokinetic
- PPE personal protective equipment
- PT prothrombin time
- PR interval time the electrical impulse takes to travel from the sinus node through the AV node and entering the ventricles; measured from the beginning of the P wave to the beginning of the QRS complex
- PV pharmacovigilance
- QC quality control
- QD Once a day
- QP qualified person
- QRS QRS complex represents ventricular depolarisation
- QT interval the time for both ventricular depolarisation and repolarisation to occur, and therefore roughly estimates the duration of an average ventricular action potential.
- QTc corrected QT interval
- QTcF corrected QT interval using Fridericia's formula
- $R^2$ coefficient of determination
- RBC red blood cell(s)
- RDW red blood cell distribution width
- REC Research Ethics Committee
- RR interval the time elapsed between two successive R waves

- RT-PCR — reverse transcription polymerase chain reaction
- s — second(s)
- SAD — Single acceding dose
- SAE — serious adverse event
- SAP — statistical analysis plan
- SAS — statistical analysis software by SAS Institute Inc., USA
- SD — standard deviation
- SG — specific gravity
- SHM — Sample Handling Manual
- SI — Statutory Instrument
- SmPC — Summary of Product Characteristics
- SOC — system organ class
- SOP — standard operating procedure(s)
- SUSAR — suspected unexpected serious adverse reaction
- $t_{½}$ — terminal elimination half-life
- TCR — T cell receptor
- TEAE — Treatment Emergent Adverse Event
- $T_{max}$ — the time to $C_{max}$
- THC — tetrahydrocannabinoids
- TMF — trial master file
- UK — United Kingdom
- USA — United States of America
- Vz/F — volume of distribution
- WBC — white blood cell(s)
- ºC — degrees Celsius
- % — percent

# 6 ETHICS

## 6.1 Research Ethics Committee or Institutional Review Board

This study protocol will be submitted to the Research Ethics Committee (REC) for review and provision of a favourable opinion. The favourable opinion of the REC must be obtained before commencement of any study procedures.

The favourable opinion is conditional upon the Sponsor registering the clinical trial in a publicly accessible database, within 6 weeks of the first participant recruited or following confirmation of an appropriate Health Research Authority (HRA) deferral.

All substantial protocol amendments must receive favourable opinion from the REC responsible for the study. Non-substantial amendments will not require prior favourable opinion by the REC.

If the study is stopped due to adverse events (AEs) it will not be recommenced without reference to the REC responsible for the study.

The outcome of the study (e.g., completed) will be reported to the REC responsible for the study within 90 days of completion of the last participant's final study procedures. In the event of the study being prematurely terminated a report will be submitted to the REC responsible for the study within 15 days.

A summary of the clinical study report will be submitted to the REC responsible for the study within 1 year of completion of the last participant's final study procedures.

The REC will be informed that Simbec-Orion is a commercial organisation and that the study is funded by Artax Biopharma Inc. The participants who take part in the clinical study will be paid for their inconvenience and have been informed that there will be no benefits gained by their participation. All potential conflicts of interest will be declared by the Investigators.

## 6.2 Ethical Conduct of the Study

The Principal Investigator shall be responsible for ensuring that the clinical study is performed in accordance with the Declaration of Helsinki (Brazil 2013) (APPENDIX 2: DECLARATION OF HELSINKI (BRAZIL, 2013). It will comply with International Council on Harmonisation (ICH) Good Clinical Practice (GCP) [2] and applicable regulatory requirements.

## 6.3 Participant Information and Consent

Potential participants who volunteer for participation in the study will be informed of the aims, methods, anticipated benefits and potential hazards of the study and any possible discomfort it may entail. Information will be given in both oral and written form and in the manner deemed appropriate by the Clinical Unit standard operating procedures (SOPs). Each participant will also be informed of his/her right to withdraw from the study at any time, for any reason.

A written explanation (participant information sheet) and informed consent form will be provided, and the participant will be allowed sufficient time to consider the study information. Prior to signing the informed consent form, the participant will be given an opportunity to discuss any issues concerning the study with an Investigator who has suitable knowledge of the study and will have all questions answered openly and honestly.

If the participant is willing to participate in the study, the informed consent form will be signed and personally dated by the participant and the person taking consent. The participant will receive a copy of the informed consent form together with the participant information sheet and the original signed informed consent form will be retained with the study records at the Investigator site. In addition, the actions and completion of the consenting process will be recorded in the participant's medical record (i.e., source document).

# 7 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The study will be performed at a single site, Simbec-Orion Clinical Pharmacology Unit. The overall responsibility for the study will rest with the Principal Investigator, Dr Annelize Koch. The Project Manager will act on behalf of the Principal Investigator to ensure the smooth and efficient running of all aspects of the study.

## 7.1 Study Personnel

**Contract Research Organisation: Simbec-Orion**

| | |
|---|---|
| Principal Investigator: | Dr Annelize Koch |
| Project Manager (Main Contact): | Adam Chessun |
| Project Manager Deputy: | Hannah Parry |
| Pharmacokinetics (PK): | Dr Danielle Francombe |
| Data Management and Statistics: | Simbec-Orion Biometrics |
| Laboratory Services: | Simbec-Orion Laboratory Services |
| IMP Management: | Dr Rebecca Price-Davies |

The Principal Investigator will delegate study-related activities according to staff responsibilities and job descriptions. This will be documented in a study-specific delegation of responsibilities form.

**Sponsor:** Artax Biopharma Inc

**Project Manager (Main Contact):** Andres Gagete

**Sponsor's Responsible Physician**: Richard Polisson

**Sponsor's Legal Representative:** Orion LR

**Monitor:** Simbec-Orion Clinical Development

**Pharmacovigilance (PV):** Simbec-Orion Clinical Development

## 7.2 Indemnity Arrangements

The Sponsor and Simbec-Orion carry insurance to pay compensation for injury, accident, ill health or death caused by participation in this study without regard to proof of negligence in accordance with the insurance and compensation in the event of injury in Phase I clinical trials 2012, guidance issued by the Association of the British Pharmaceutical Industry (ABPI), the BioIndustry Association (BIA) and the Clinical Contract Research Association (CCRA) in consultation with the Department of Health (DoH) and the National Research Ethics Service (NRES).

# 8 INTRODUCTION

## 8.1 Summary

Artax Biopharma Inc is developing AX-158, a new chemical entity (NCE), for the treatment of autoimmune and inflammatory diseases such as psoriasis, multiple sclerosis, rheumatoid arthritis, and Crohn's disease. These are diverse groups of diseases in which the adaptive immune system (particularly via T lymphocytes) attacks self-antigens in the body. These diseases are extremely relevant from both a social and economic point of view since their high incidence and chronic nature, represents a significant socio-economic burden for communities worldwide.

The AX-158 therapeutic target is the T cell receptor (TCR) signalosome. The compound, through its direct interaction with Nck1, a component of the signalosome, selectively modulates self-directed T cell activation which is a cause of autoimmune disease.

T cells can recognise foreign and self-antigens and trigger the immune response against them. Recognition of the antigen by the T cell is carried out by the TCR responsible for signal transmission to the cytoplasm. To become active, reactive T cells have to receive three signals:

- **Signal 1**, derived from the **TCR** after antigen recognition. This signal is the initiation event of the immune response and the most relevant one.
- **Signal 2**, derived from co-stimulatory receptor (CD28).
- **Signal 3**, derived from cytokine receptors, which are responsible for T cell proliferation and differentiation into different types of effectors.

T cells are a critical element of immunopathological response mechanisms. AX-158 is designed to centrally address autoimmune diseases by modulating the response of T cells by changing the strength of low avidity TCR signalling events that are responsible for T cell activation in autoimmune diseases while not interfering with normal strong responses to foreign antigen challenges.

AX-158 did not suppress acute immune responses in pre-clinical murine models involving either the immune-dominant vaccinia peptide B8R or haptenated antigens. However, the effect of AX-158 on human immune surveillance, including the response to vaccination, is unknown.

## 8.2 Physical, Chemical and Pharmaceutical Properties and Formulation

AX-158 is a dark brown crystalline powder. The drug substance is filled into size 2 capsules which contain a minimum of 5 mg of AX-158 (dose assembled into single capsules per dose level for each cohort). The capsules are for oral administration.

Please refer to the current version of the Investigators Brochure (IB)[1] and Investigational Medicinal Product Dossier (IMPD)[3] for detailed information about the pharmaceutical

properties, formulation, and data (including pharmacology and toxicology data) derived from the non-clinical investigations of AX-158.

## 8.3 Nonclinical Pharmacology

*In vitro* studies have demonstrated activity of AX-158 at key points in the T cell TCR signaling cascade (proximal to the TCR, at key integrator of TCR signaling Akt, and at resulting cytokine production).

Rapid phosphorylation of ZAP70 (pZAP70) in human Jurkat cells was observed upon TCR stimulation with Anti-CD3 (OKT3) and assessed by commercial HTRF (homogenous Time Resolved Fluorescence) methodology (Cisbio). Treatment of cells with AX-158 potently modulated pZAP70 signaling.

Rapid phosphorylation of Akt (S473) was observed in primary T cells (PBMC) using flow cytometry analysis to study impacted T cell subsets. AX-158 potently impacts phosphorylation of Akt (S473) in both CD4+ and CD8+ T cells following stimulation (Anti-CD3 / CD28).

Cytokine production in primary T cells (PBMCs) was stimulated by Anti-CD3 activation of the TCR and assessed by flow cytometry. AX-158 potently modulated IL-2 production in CD4+ T Cells. AX-158 reduces intracellular IL-2 in primary CD4+ T cells following Anti-CD3 stimulation of PBMCs as assessed by flow cytometry.

## 8.4 Nonclinical Pharmacokinetics

The results of safety pharmacology studies indicate that AX-158 has no effects on physiological, respiratory and CNS up to the maximum dose tested 180 mg/kg in rats, which is nearly 375 times the equivalent efficacy dose (1 mg/kg) on a body surface area basis in the EAE mouse model.

The *in vitro* study on hERG clone cells showed that AX-158 is a week inhibitor of the hERG channel. The IC50 is 145 times higher than the peak free plasma concentration at the efficacious dose in EAE mouse model.

Regarding *in vivo* cardiovascular parameters, a preliminary dog telemetry study was conducted in three unanaesthetised male beagle dogs and comprising three oral treatment groups: control (vehicle), 2 mg/kg AX-158 and 20 mg/kg AX-158. AX-158 at the dose of 2 mg/kg and 20 mg/kg did not affect heart rate, body temperature and ECG parameters when compared to the vehicle. At the low dose of 2 mg/kg, no changes in mean, systolic, and diastolic arterial blood pressure were observed. At the high dose of 20 mg/kg, a statistically significant increase in diastolic arterial blood pressure was observed in each of the 3 test animals (mean 38% maximal increase from pre-dose baseline and 26% higher compared to vehicle treatment), which in each case resolved by 16 hours post-dosing. No noticeable change in the sympatho-vagal balance attributed to AX-158 was seen at either dose. Dosing confirmation samples indicated that the plasma concentration at 20 mg/kg dose level was 4.5 µg/mL at 4 h post dose.

In view of this unexpected finding, an extended battery of haemodynamic and cardiovascular studies was performed, including: a non-good laboratory practice (GLP) telemetry study in conscious dogs via IV dosing 10 mg/kg (estimated peak plasma concentration: 18-20 µg/mL), a non-GLP study in anaesthetised rats via IV dosing up to 9 mg/kg (plasma concentration not measured, however rats given at 2 mg/kg IV showed peak plasma concentrations around 12 µg/ml then it could be estimated that rats given 9 mg/kg would have been exposed at least at 3-4 times this concentration ), a non-GLP telemetry study in conscious minipigs via oral dosing up to 100 mg/kg (measured peak plasma concentration: 3.3 µg/mL) and a GLP telemetry study in conscious minipigs via oral dosing up to 300 mg/kg (estimated peak plasma concentration: 14 µg/ml). None of the studies showed any change of biological significance in heart rate, arterial blood pressure or electrocardiographic activity. The increase in blood pressure observed in dogs via oral dosing at 20 mg/kg could not be reproduced.

Collectively, data from 4 studies in 3 different species did not show changes in blood pressure even at doses that resulted in peak plasma concentrations 3-4 times the concentration achieved in the dog study where blood pressure was increased. Therefore, the accumulated data allows suggesting that the effect observed in dogs was incidental and non-reproducible.

Overall, single oral and intravenous dose studies were performed in several species to characterise its pharmacokinetics and bioavailability of AX-158. The bioanalytical methods for rat and minipig were validated according to FDA and EMA guidelines for the toxicokinetic assessment incorporated in the repeated dose toxicology studies. Plasma *in vitro* protein binding was determined in the species used in the preclinical studies and in human. AX-158 metabolic profile was evaluated *in vivo* in rat, dog, minipig and in vitro using primary hepatocyte in humans and no *in vitro* CYP inhibition was observed.

## 8.5 Toxicology

In rats the maximum tolerated dose (MTD) following three consecutive days of oral administration of AX-158 was determined to be 300 mg/kg/day. A subsequent dose range finding study was conducted with doses up to 180 mg/kg/day for 14 days whereby the MTD was determined to be 180 mg/kg. A 28-day GLP toxicity study was carried out with doses up to 180 mg/kg/day by oral route. The studies elicited a decrease in the size of testes, epididymides, seminal vesicles and coagulating glands at doses ≥ 50 mg/kg/day. The changes in testes and epididymides were microscopically associated with degeneration/atrophy of seminiferous tubules of testes and cell debris/decreased sperm in lumen of epididymides. However, there were no associated microscopic changes in seminal vesicles and coagulating glands. These changes were observed to be partially reversible in recovery animals. Test item related perivascular inflammation at the base of heart involving the tunica adventitia of aorta and surrounding brown adipose tissue was noted at ≥50 mg/kg/day in both sexes and a single incidence in recovery group female animal. Chronic inflammation was observed with the presence of mononuclear cells and fibroblasts. The NOAEL in rat in the 28-day study was 15 mg/kg/day.

In minipigs, a MTD study achieving doses up to 600 mg/kg was performed by oral route. The MTD was >600 mg/kg. A 14 days DRF study was subsequently performed at 300 and 600 mg/kg. The MTD following 14 consecutive days of oral administration was considered to be

300 mg/kg/day. A 28-day oral repeated dose study was performed at 30, 100 and 300 mg/kg/day with 14 days of recovery period (Study A3674). The NOAEL in females was defined at the highest dose tested (300 mg/kg/day), while treatment-related reduction in the absolute and relative testes weight, correlated with treatment-related microscopic observations such as testicular hypoplasia/atrophy were observed in all male animals and not normalized after the recovery period. A second 28-day oral study only in males at 5, 15, and 50 mg/kg/day with a 10 week recovery period has been performed accordingly at lower doses in order to determine the NOAEL (Study A4211). As referenced in the histopathological report, testicular hypoplasia/atrophy is a common finding in male minipigs that appears in a spontaneous manner making it difficult to discriminate between test item-related effects and background noise from the species. For that reason, in the new study a few modifications were made to tackle this issue:

- Higher number of animals per group were used (increased from 3 to 5) in order to provide additional statistical power to the study.
- In addition, animals included on the study were screened using ultrasound to discard those showing detectable testicular damage/alteration.
- Finally, this study included animals one month older than those from the previous GLP study in order to maximize the chances of them reaching sexual maturity.

As a result, findings were observed at all dose levels in this new study were indistinguishable from those of including the control group and therefore where testicular alterations where indeed more severe than those on the treated animals. Therefore, considered not treatment related but incidental. Recovery animals also showed no alterations. Accordingly, the highest dose level at 50 mg/kg was selected as the NOAEL.

It is important to note that current NOAEL is higher than the previous GLP study LOAEL which was defined at 30 mg/kg. In addition, the 50 mg/kg (NOAEL) and the 30 mg/kg (LOAEL) levels from the two different studies showed similar exposures in terms of $AUC_{last}$ at the end of the treatment (66.72 µg.h/mL and 60.101 µg.h/mL respectively) and yet it was not possible to reproduce the testicular damage on the second GLP study at 50 mg/kg.

Overall, minipig NOAEL definitions are presented as follows merging the available data from the two GLP studies:

- Female NOAEL for minipig was stablished at 300 mg/kg, the highest dose examined in the first GLP study.
- For the male minipig, testicular findings were considered as treatment related in study A3674 because of an apparent dose-dependent relationship. However, in study A4211 with added statistical power and pre-screening of animals for sexual maturity, findings were considered an expression of spontaneous and/or incidental pathology.
- Although the results of both studies allow the assumption that findings in testes observed in study A3674 could be regarded as spontaneous and within the biological interindividual variability, there is not sufficient information at this time to discard a treatment related effect, as in rats, therefore an overall NOAEL of 15 mg/kg/day is selected, which results from the integrated assessment of the 2 minipig studies.

A complete standard genotoxicity package according to ICH M3 was performed, demonstrating that AX-158 was not mutagenic in the Bacterial Reverse Mutation Assay up to the highest recommended concentration of 5000 µg/plate. AX-158 was neither clastogenic up to the maximum non-cytotoxic concentration of 27 µg/mL in cultured human peripheral blood lymphocytes, either in the presence or in the absence of metabolic activation, higher concentrations showed remarkable cytotoxicity. Finally, AX-158 did not induce significant increases in micronucleated PCE in male and female Sprague Dawley rats when orally administered up to the MTD (500 mg/kg/day).

On the basis of the above, the defined exposure limits for this study are set as the following: $C_{max}$ = 3.26 µg/mL & $AUC_{0-24}$ = 14.859 µg*h/mL.

## 8.6 Clinical Experience

There has been no clinical experience with AX-158 to date. AX-158-101 is a first in human (FIH) clinical study.

## 8.7 Risk Assessment

The risk of this proposed Phase I study is considered acceptable given that:

- There were no adverse events seen in non-clinical species above the NOAEL which warrant specific monitoring of participants.
- The proposed starting dose of AX-158 in humans (5 mg/day) is 29 times lower than the HED of NOAEL from the most sensitive species (the rat) and the starting dose is predicted to achieve total exposures 3x-fold lower than the lowest efficacious exposure achieved in the mouse at 1 mg/kg, an approximately 121-fold lower total $C_{max}$, and 69-fold lower total AUC than exposure achieved at the NOAEL in rats and 78-fold lower total male $C_{max}$, and 41-fold lower total AUC than exposure achieved at the NOAEL in minipigs.
- The starting dose in Part C (multiple ascending dose [MAD]) will not exceed the highest dose examined in the preceding completed Part A (single ascending dose [SAD]) cohorts or a level expected to exceed the highest AX-158 exposure ($C_{max}$ and $AUC_{0-24}$) observed from preceding Part A (SAD) cohorts.
- For each SAD and MAD cohort, 2 sentinel participants (1 active, 1 placebo) will be dosed and monitored for 24 h prior to dosing the rest of the cohort.
- In Part A (SAD), dose escalation will be done in a stepwise, controlled manner, with dose escalation only being permitted after full evaluation of up to 24 h PK and 72 h safety data from the previous cohort by the Dose Escalation Review Committee (DERC).
- In Part C (MAD) dose escalation will be done in a stepwise, controlled manner, with dose escalation only being permitted after full evaluation of up to 10 days PK and safety data from the previous cohort by the DERC.
- The study is being conducted in a Medicines and Healthcare products Regulatory Agency (MHRA) accredited Phase I unit.

Further details of the non-clinical studies and a summary of the known and potential risks and benefits to human participants of AX-158 can be found in the Investigator's Brochure (IB)[2].

The study will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s), as indicated within Section 6.2.5 of the ICH GCP E6 (R2) guidelines[2].

## 8.8 Coronavirus Disease 2019 (COVID-19) Risk/Benefit Assessment

This study is to be conducted in healthy adult participants who are deemed not to be at higher risk of COVID-19 as per the latest version of the National Health Service (NHS) Guidance (https://www.nhs.uk/conditions/coronavirus-covid-19/people-at-higher-risk/whos-at-higher-risk-from-coronavirus/.

The safety of the participant is the primary concern; this study is to be conducted at Simbec-Orion Clinical Pharmacology Unit which is a Phase I accredited unit with extensive experience in conducting Phase I trials of similar design. Simbec-Orion prioritise the health and wellbeing of their clinical trial participants and, as such, have implemented a number of COVID-19 policies and risk mitigating actions. Prior to attendance at site, participants will be contacted to ensure they are not displaying any COVID-19 symptoms; Site COVID-19 policies will be explained to them at this time. Where appropriate perspex screens are in place and appropriate social distancing is enforced, when this is not possible, appropriate personal protective equipment (PPE) will be worn.

Simbec-Orion Clinical Pharmacology unit is a dedicated trial facility and, as such, staffing levels will not be affected by the potential burden presented by COVID-19 to other medical facilities. All employees present at the clinical site are aware of the COVID-19 specific working requirements and will work to the relevant 'Working Safely' Policy.

Medicines and Healthcare products Regulatory Agency (MHRA) Phase I Accreditation requirement No. 3 details the requirement for an agreement with a local hospital for supporting emergencies arising from the clinical trials performed by Simbec-Orion, this agreement is in place with Cwm Taf Morgannwg University Health Board and Prince Charles Hospital (PCH) for this purpose. Cwm Taf Morgannwg University Health Board and PCH have confirmed capacity to support any acute serious AEs (SAEs) during the COVID-19 pandemic (details contained within the latest version of the Simbec-Orion Clinical General Risk Assessment.

AX-158 did not suppress acute immune responses in pre-clinical murine models involving either the immune-dominant vaccinia peptide B8R or haptenated antigens. However, the effect of AX-158 on human immune surveillance, including the response to vaccination, is unknown. All participants will remain in-house for the duration of the study under the medical supervision of the PI throughout.

In addition, the sponsor has conducted a risk assessment in consideration of the ongoing COVID-19 vaccine deployment programme including assessment of the potential risks associated with concomitant vaccination whilst participating in this trial.

The sponsor has determined that the outcome of the risk assessment undertaken in conjunction with the study team is as follows. Knowledge on the Investigational Medicinal Product (IMP) is currently insufficient to assess the potential impact of IMP on the efficacy of COVID-19 vaccination or to assess the impact of COVID vaccination on IMP safety. If given concomitantly, it could possibly be difficult to discriminate if the AEs observed during the study are due to the IMP or due to COVID-19 vaccine. In addition, the study participants are young healthy volunteers, by definition without any co-morbidity, and are in consequence in a category of subjects without any immediate risk of developing a severe form of COVID-19, and not considered the top priority for the UK vaccine campaign.

Therefore, participants will be required to be fully vaccinated according to current Welsh / UK government guidelines prior to admission into the study. Participants are not permitted to have their COVID-19 vaccine injections (boosters) whilst in the study (from 28 days prior to dosing to completion of final post-study follow up procedures). Participants will be informed that if they are invited to receive a COVID-19 vaccination during the study and wish to receive the vaccine that they will be withdrawn from participation in the study. The investigator will check that any participants who may have a pre-booked appointment for a COVID-19 vaccination, are not in breach of this requirement.

Both the Study and Site Risk Assessments will be continually monitored and updated throughout the trial, and it is currently deemed acceptable to conduct the trial without it impacting or being impacted by the COVID-19 pandemic.

# 9 STUDY OBJECTIVES

## 9.1 Primary Study Objective

- To assess the safety and tolerability of single and multiple ascending doses of AX-158 when administered to healthy participants (Part A and Part C).

## 9.2 Secondary Study Objective

- To investigate the PK of single and multiple doses of AX-158 in healthy participants (Part A and Part C).
- To investigate any food effect on the PK of AX-158 following oral administration of a single dose to healthy participants (Part B).

# 10 INVESTIGATIONAL PLAN

## 10.1 Overall Study Design and Plan

This is a phase I, randomised, double-blind, placebo-controlled study to investigate the safety, tolerability, and PK of AX-158 in healthy male participants following single (Part A) and multiple (Part C) ascending doses including food effect (Part B).

The study will be conducted in three parts (Part A, Part B and Part C).

Part A (SAD) will enrol 8 participants per cohort randomised (3:1) to receive AX-158 (6 participants) or placebo (2 participants). Part A will follow a single ascending dose (SAD) design with all participants receiving one dose of AX-158 (or placebo) in the fasted state. Part B (Food Effect) will be conducted in 8 participants in a cross-over manner; each participant will receive AX-158 in the fed and fasted state. Part C (MAD) will enrol 8 participants per cohort randomised to (3:1) to receive AX-158 (6 participants) or placebo (2 participants).

Part C will follow a MAD design with participants receiving AX-158 (or placebo) once daily for 10 consecutive days, in a fed or fasted state (depending on the outcome of the Part B Food Effect). Doses, dosing duration and dose regimen (i.e., q.i.d., b.i.d., t.i.d.) of AX-158 and matching placebo for Part C may be modified based on all available safety, tolerability, and PK data and applied to additional MAD cohorts.

Up to one hundred and four (104) healthy participants are planned to be enrolled in this 3-part, multi cohort study. Part A (SAD) will be conducted in up to forty (40) participants (5 cohorts of 8 participants). Part B (Food Effect) will be conducted in 8 participants in a cross-over manner. Part C (MAD) will be conducted in up to twenty-four (24) participants (3 cohorts of 8 participants). Each participant will be assigned to only one study part and within each part, assigned to only one cohort.

Participants in Part A (SAD) will undergo a screening period (Day -28 to Day -2), an in-house treatment period comprising 4 overnight stays (from Day -1 to Day 4) and a follow up visit 5-7 days following administration of AX-158 or placebo.

Participants in Part B (Food Effect) will undergo a screening period (Day -28 to Day -2), two in-house treatment periods comprising of 4 overnight stays (from Day -1 to Day 4) separated by a minimum of 7 days between doses and a follow up visit 5-7 days following the final administration of AX-158.

Participants in Part C (MAD) will undergo a screening period (Day -28 to Day -2), an in-house treatment period comprising 13 overnight stays (from Day -1 to Day 13) and a follow up visit 5-7 days following the final administration of AX-158 or placebo.

For Part A (SAD) and Part C (MAD), a dose leader design will be implemented with 2 participants being dosed on the first dosing day of each cohort. Of these 2, 1 will be on active drug and 1 on placebo. The remainder of the cohort will be dosed at least 24 h later pending an acceptable safety profile in the dose-leader group and will contain at least 1 additional placebo participant. This design allows maintenance of the “blind” while also staggering ongoing exposure within the MAD phase.

In both Part A (SAD) and Part C (MAD), sequential cohorts will be exposed to increasing doses of AX-158. Prior to dose escalation between cohorts, safety and PK data from the previous

cohort will be reviewed by the DERC to determine whether it is appropriate to proceed to the next cohort/dose level.

The maximum dose level administered will not exceed a level anticipated to result in plasma exposures greater than those seen at the NOAEL, without prior approval by the REC and MHRA, as per Section 6.4.4 of the ICH E6 (R2) guidelines[2].

The clinical phase is anticipated to take place between September 2021 and May 2022. The conclusion of the study is defined as last participant last visit.

The study will take place in the Clinical Unit of Simbec-Orion Clinical Pharmacology (Clinical Unit) under full medical and nursing supervision.

A schedule of all study assessments is provided in Table 10.9.1, Table 10.9.2 and Table 10.9.3.

**Part A (SAD)**

Up to 5 dose levels of AX-158 are planned to be investigated in Part A of the study (with an option to include additional dose levels to a maximum of 2 cohorts). Each cohort will follow a dose-leader schedule; two participants (one randomised to receive placebo and one randomised to receive AX-158) will be dosed in a blinded manner at least 24 hours prior to the remainder of the cohort. In the absence of any safety concerns in these first 2 participants, dosing of the remainder of the cohort will proceed on a parallel study schedule.

The lowest dose of AX-158 will be evaluated first; refer to Section 10.8.7 for further details; dose administration in the subsequent cohort will only proceed after blinded review of available safety and PK data from a minimum of six (6) evaluable participants in the preceding cohort by the DERC; see Section 10.3 for full details. The maximum dose investigated will not exceed a level anticipated to result in a $C_{max}$ or $AUC_{0-24}$ exceeding those observed at NOAEL levels in the most relevant non-clinical species without prior approval by the REC and MHRA (via substantial amendment). The study may be discontinued at any time if any unacceptable safety findings are identified (as determined by PI and Sponsor).

**Screening (Days -28 to Day -2)**

Screening assessments will be performed from Day -28 to Day -2 to ensure the eligibility of participants. Assessments will be performed as per Table 10.9.1

**Treatment Period (Day -1 to Post-Treatment 3 (i.e., Day 4))**

Participants will be admitted to the Clinical Unit on the morning of Day -1 with confirmation of eligibility and baseline assessments performed as per Table 10.9.1. Randomisation will occur prior to dose on Day 1.

After an overnight fast of at least 10 h, dose administration will occur on the morning of Day 1. Fasting will continue until 4 h post-dose; a standardised meal will then be provided. Clinical and laboratory assessments of safety, tolerability and PK variables will be conducted throughout the in-house period as per Table 10.9.1. Participants will be discharged from the clinical unit following completion of 72 h post-dose assessments providing there are no ongoing safety concerns; participants may be monitored as an outpatient where the PI (or delegate) deems this to be appropriate.

A follow-up visit will be conducted 5-7 days following the first dose of AX-158 or placebo (i.e., Day 8) as per Table 10.9.1.

**Post-Study Follow Up Visit (5-7 days after last dose of IMP (i.e., Day 8)).**

For participants in all SAD cohorts, a follow-up visit will be conducted 5-7 days following last IMP or placebo administration (i.e., Day 8). If all follow-up assessments (Table 10.9.1) are satisfactory the PI (or delegate), will discharge the participant from the study. If any AEs are ongoing, or any assessments are not satisfactory, participants may be recalled to the unit for follow-up assessments until the PI (or delegate) is satisfied the participant is medically stable and may be discharged from the study. Participants will be advised to return or contact the unit at any time if they may be experiencing any adverse effects.

Following DERC review of data from Part A, the dose for participants in Part B will be determined.

**Part B (Food Effect)**

The dose to be evaluated in the food-effect cohort will be determined based on review of all available safety, tolerability, and PK data from Part A. Participants in the food-effect cohort will receive AX-158 administered under both fasted and fed conditions.

Where receiving a dose in the fed state, participants will be provided the standard FDA high fat breakfast[5] which should be consumed within 30 minutes (mins) or less, with study drug administration occurring approximately 30 mins after the start of the meal. Fasting will recommence until 4 h post-dose; a standardised meal will then be provided.

Participants will be discharged from the clinical unit following completion of 72 h post-dose assessments providing there are no ongoing safety concerns; participants will be monitored as an outpatient.

**Treatment Periods (Day -1 to Day 4):** Participants will receive a single dose of AX-158 over 2 treatments periods in fed/fasted conditions (1 condition per period). Each treatment period will be approximately 4 days duration, from the morning before dosing (Day -1) until 72 h post-dose (Day 4). During each treatment period, participants will receive a single dose of AX-158 following an overnight fast of at least 10 h OR following consumption of a high-fat breakfast over 2 treatment periods (1 per period). When receiving AX-158 in the fed state, following an overnight fast of at least 10 h, participants will be provided the standard FDA high fat breakfast which will be served and consumed within 30 mins. AX-158 should be administered 30 mins after the start of the meal. At both treatment periods, fasting will continue/recommence until 4 h post-dose; a standardised meal will then be provided. Participants will be discharged 72 h post-dose. PK samples will be collected pre-dose and up to 72 h post-dose for the measurement of AX-158. Safety will also be evaluated at time points specified in Table 10.9.2. There will be at least 7 days between dose administrations.

Following DERC review of data from Part B, the dose for participants in Part C will be determined, and cohorts in Part C may be administered AX-158 under fasted or fed conditions as deemed appropriate, pending DERC determination of any appreciable impact of food on the absorption, distribution, metabolism, and excretion (ADME) of AX-158.

A follow-up visit will be conducted 5-7 days following last IMP administration. If all follow-up assessments (Table 10.9.2) are satisfactory the PI (or delegate), will discharge the participant from the study. If any AEs are ongoing, or any assessments are not satisfactory, participants may be recalled to the unit for follow-up assessments until the PI (or delegate) is

satisfied the participant is medically stable and may be discharged from the study. Participants will be advised to return or contact the unit at any time if they may be experiencing any adverse effects.

**Part C (MAD)**

Part C will be initiated following review of all available safety, tolerability, and PK data from Part A (SAD) and Part B (Food Effect) to determine the appropriate AX-158 dose and dosage regimen to be evaluated in the initial MAD cohort; the starting dose in Part C will not exceed the highest dose level examined in the preceding completed Part A cohorts or a dose level expected to exceed the highest AX-158 exposure ($C_{max}$ and $AUC_{0-24}$) observed from preceding Part A cohorts. It is planned to dose AX-158 or placebo once daily for at least 10 consecutive days; doses, dosing duration and dose regimen (i.e., q.i.d., b.i.d., t.i.d.) of AX-158 and matching placebo for Part C may be modified based on all available safety, tolerability, and PK data and applied to additional MAD cohorts. The maximum dose will not exceed a level anticipated to result in a $C_{max}$ or $AUC_{0-24}$ exceeding those observed at NOAEL levels in the most relevant non-clinical species without prior approval by the REC and MHRA (via substantial amendment).

Up to 3 dose levels of AX-158 are planned to be investigated in Part C of the study (with an option to include additional dose levels to a maximum of 2 cohorts). Each cohort will follow a dose-leader schedule in which two participants (one randomised to receive placebo and one randomised to receive AX-158) will be dosed at least 24 h prior to the remainder of the cohort allowing for review of emerging safety and tolerability data from this dose-leader group on an ongoing basis and to avoid dosing all participants in a cohort simultaneously.

The lowest dose level of AX-158 will be evaluated first; dose administration in the subsequent cohorts will only proceed after blinded safety, tolerability, and PK data from a minimum of 6 evaluable participants in the preceding cohort have been reviewed by the DERC; see Section 10.3 for full details). The study part may be discontinued at any time if any unacceptable safety findings are identified (as determined by PI and Sponsor).

**Screening (Days -28 to Day -2)**

Screening assessments will be performed from Day -28 to Day -2 to ensure the eligibility of participants. Assessments will be performed as per Table 10.9.3.

**In-patient Period (Day -1 to Post-Treatment 3 (i.e., Day 13))**

Participants will be admitted to the Clinical Unit on the morning of Day-1 with confirmation of eligibility and baseline assessments performed as per Table 10.9.3. Randomisation will occur prior to dose on Day 1. An evening snack will be consumed at least 10 h before each dose administration. After an overnight fast of at least 10 h, dose administration will occur each day, on the morning of Day 1 to Final Dosing Day (planned as Day 10). It is planned to administer doses in Part C in a fasted state, however following review of Part B food-effect data, the dose *may* be administered in a fed state with a standardised meal. Fasting will continue until 4 h post-dose; a standardised meal will then be provided. Clinical and laboratory assessments of safety, tolerability and PK variables will be conducted throughout the in-house period as per Table 10.9.3.

Participants will be discharged from the Clinical Unit on Post-Treatment (i.e., Day 13) following the completion of the 72 h post-last dose assessments providing there are no ongoing safety concerns.

**Post-Study Follow Up Visit (5-7 days after final dose of IMP i.e., Day 17).**

For participants in all MAD cohorts, a follow-up visit will be conducted 5-7 days following last IMP or placebo administration. If all follow-up assessments (Table 10.9.3.) are satisfactory the PI (or delegate), will discharge the participant from the study. If any AEs are ongoing, or any assessments are not satisfactory, participants may be recalled to the unit for follow-up assessments until the PI (or delegate) is satisfied the participant is medically stable and may be discharged from the study. Participants will be advised to return or contact the unit at any time if they may be experiencing any adverse effects.

## 10.2 Adaptive Elements

This study is designed to be adaptive, and the following elements may be revised based on emerging clinical safety and PK data throughout the course of the trial without a substantial amendment:

- Following review of the Part B Food effect cohort PK data, participants in Part C cohorts may be administered AX-158 under fasted or fed conditions, as deemed appropriate, pending DERC determination of any appreciable impact of food effect of AX-158. If food effect is seen, cohorts in Part C could be dosed with a standardised meal (as opposed to the high-fat breakfast). This decision will be documented in the Food Effect Cohort Dose Escalation Review meeting minutes.
- The timing, type, and number of safety, PK assessments may be modified (without extending the duration of the study).
- A minimum washout of 7 days is expected within Part B but *may* be extended based on emerging safety and PK data to 14 days.
- The number and/or volume of blood samples per assessment may be increased as long as the total volume of blood drawn for a participant does not exceed 10% of the pre-specified total blood volume or surpass 500 mL (except when extra blood samples need to be taken for safety reasons).
- In Part C (MAD), it is planned to dose AX-158 or placebo once daily for at least 10 consecutive days; doses dosing duration and dose regimen (i.e., q.i.d., b.i.d, t.i.d) of AX-158 and matching placebo for Part C *may* be modified based on all available safety, tolerability, and PK data and applied to additional MAD cohorts up to a maximum of 14 days.
- Dose levels/dosing regimen *may* be adjusted **lower** based on emerging safety and PK data.
- Additional dose level(s) *may* be examined if deemed safe and appropriate. These cohorts will enrol 8 participants (for SAD cohorts) and up to 8 participants (for MAD cohorts).
- Currently it is planned that in order to dose escalate between cohorts and between study parts, PK data from up to the 24 hr post-last time point in all parts and 72 hr post-last dose safety data is required. However, if during the course of dose escalation, it is

determined necessary to do so, then dose escalation procedures may be extended in order to include additional PK data up to the 72 hr post-last dose time point in all study parts.

- Exploratory PD samples will be taken pre-dose in Part A (SAD) and Part C (MAD) additional sample(s) will be taken based on emerging data. The total blood volume will not exceed 500mL.

## 10.3 Dose Escalation Procedures and Stopping Criteria

### 10.3.1 Dose Escalation Procedures

Following completion of each cohort, a summary of all relevant safety AEs, ECG, vital signs, laboratory assessments up to 72 h post dose) and PK data (up to 24 h post-dose for Part A & Part B and 10 days for Part C) will be produced on behalf of the Principal Investigator. Planned doses may be modified following a review of emerging data. Progression to the next SAD dose level and dose selection will be based on the available safety and PK data from at least 6 evaluable participants from the preceding dose level. Progression to the next MAD dose level and dose selection will be based on the available safety and PK data from at least 6 evaluable participants from the preceding dose level. An evaluable participant is defined as a participant who has received the planned dose (active or placebo) and has sufficient PK samples to estimate $C_{max}$ and $AUC_{0-24}$. Dose escalation will be dependent upon generation of acceptable safety (and PK) data. If it is not appropriate to escalate the dose according to the proposed dose escalation schedule, then the same dose, an intermediate dose or a lower dose may be given following discussion between the Sponsor and the Principal Investigator (or deputy) if no stopping criteria are met.

There will be a Telephone Conference at a pre-appointed time to involve the Simbec-Orion Project Manager and Principal Investigator (or deputy) and the Sponsor's representative(s), including the Sponsor's Responsible Physician. After discussion of all the data, the decision will be made whether to dose escalate and a written document (dose escalation approval form) signed by the Principal Investigator (or deputy) and Sponsor will be produced ratifying that decision. Full minutes, to be agreed by all parties, will be produced for each discussion regarding dose escalation and filed in the Investigator Site File. A copy of the signed dose escalation approval form will be provided to the Simbec-Orion IMP Management team to allow the release of the next dose level of IMP to the clinic.

Dose escalation stopping criteria are detailed in Section 10.3.4

### 10.3.2 Stopping Criteria

### 10.3.3 General Stopping Criteria

The study will be discontinued if any unacceptable safety findings are identified. This decision will be made jointly by the Principal Investigator (or deputy) and the Sponsor. A written document signed by the Principal Investigator (or deputy) and Sponsor will be produced ratifying the decision.

Individual participants may also be withdrawn for any of the reasons outlined in Section 10.7.4.

### 10.3.4 Progression from Dose Leader Group/Dose Escalation Stopping Criteria

If any of the below-listed criteria are met, further dosing or dose escalation between cohorts will be temporarily stopped pending evaluation of all available data:

- 'serious' adverse reaction (i.e., a serious adverse event considered related to the IMP administration) in one participant, as defined in Section 10.9.11.
- 'severe' non-serious adverse reactions (i.e., severe non-serious adverse events considered related to the IMP administration) in two participants in the same cohort, independent of within or not within the same system-organ-class, as defined in Section 10.9.11.
- 4 out of 8 participants in a cohort experience the same moderate or severe AE that is considered related to the IMP.
- 1 or more participant in the cohort experiences a drug related SAE.
- Any participant experiences a severe AE in any key safety variable (ECG, laboratory safety or vital signs) that in the opinion of the Investigator is at least possibly related to the IMP and may jeopardise the safety of the participants.
- QTcF < 330 ms, QTcF > 500 ms or a QTcF increase of > 60 ms in any participant confirmed on 3 consecutive ECGs, at least 1 min a part.
- Systemic exposure ($C_{max}$ and AUC) for a dose that is anticipated to exceed pre-determined exposure limits based on preclinical toxicology data and/or already available human PK data i.e., $C_{max}$ = 3.26 µg/mL & $AUC_{0-24}$ = 14.859 µg*h/mL.
- Any other toxicity which in the opinion of the Principal Investigator and the medical monitors of CRO and Sponsor would preclude dosing additional participants at the indicated dose level.
- Any of the following elevation in a liver function test result, must have a possible relationship to IMP, to be confirmed on repeat samples, and other potential causes (i.e., strenuous exercise, use of a concomitant medication, viral infection such as hepatitis A or cytomegalovirus) must have been excluded.
    - ALT or AST >3x ULN and (BIL-T >2x ULN or INR >1.5) *
    - ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) *

**Dependent on availability of liver function test data, observation may be made following progression from dose leader group. Any findings and impact will be reviewed and implemented (where applicable) immediately.*

Individual participants may also be withdrawn for any of the reasons outlined in Section 10.7.4.

If any of the above criteria are fulfilled, dose escalation will only proceed once an appropriate substantial amendment has been submitted and receives regulatory approval from the MHRA and approval from the REC associated with the study.

## 10.4 Discussion of Study Design, including the Choice of Control Groups

This study will be conducted in three parts (Part A [SAD], Part B [Food Effect] and Part C [MAD]). Part A is a randomised, double-blind, placebo-controlled SAD study to assess the safety, tolerability, and pharmacokinetics of AX-158 in up to 40 healthy male participants. Two additional cohorts of 8 participants each may be investigated if required. Part B is a randomised two-way cross over food effect study of AX-158, participants will receive a single dose of AX-158 in both the fed and fasted state to assess safety, tolerability, pharmacokinetics of AX-158. Part C is a randomised, double-blind, placebo-controlled MAD study to assess the safety, tolerability, and pharmacokinetics of AX-158 in up to 24 healthy male participants. Two additional cohorts of 8 participants each may be investigated if required. The study employs a SAD parallel-group design; corresponding placebo control will be administered in order to evaluate treatment-related effects. Safety and PK data from a minimum of 6 participants of each cohort will be required for data review prior to dose escalation.

The design of this study is typical of that used for FIH studies with a "dose leader" design for built-in safety. A dose leader design will be implemented in which 2 participants (1 AX-158 and 1 placebo) in each cohort will be dosed approximately 24 h before the remainder of the Cohort. Providing there are no safety concerns in the dose leader group (to the 24 h time-point), the remainder of the cohort (6 participants) will be dosed a day later and will be randomised in such a way that at least one further participant receives placebo. This design allows maintenance of the "blind" and is intended to reduce the number of participants simultaneously exposed to risk in order to better manage the safety aspects of the trial.

## 10.5 Selection of Study Population

Up to one hundred and four (104) participants are planned to be enrolled into Part A, B and C of the study.

The study is to be conducted in healthy male participants; therefore, participants are not expected to derive any therapeutic benefit from taking part in the study. A healthy participant population with carefully considered inclusion/exclusion criteria will avoid the potential for interaction of AX-158 with any underlying disease state or concomitant medication that it may be necessary for patients to take, while ensuring that participants are fit and well enough for participation in the study.

AX-158 has not been previously administered to humans; therefore, its effects in humans are as yet unknown.

The following eligibility criteria are designed to select participants for whom protocol treatment and procedures are considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular participant.

Deviations from inclusion and exclusion criteria are not allowed as deviations have the potential to impact the scientific integrity of the study, regulatory acceptability or participant safety as such deviations constitute a deliberate breach of Regulation 29 of Statutory Instrument (SI) 2004/1031. Therefore, adherence to the criteria as specified in the protocol is essential.

### 10.5.1 Inclusion Criteria

**To be confirmed at screening:**

1. Healthy Male participant, between 18 and 50 years of age, inclusive.
2. Male participant (and partner of childbearing potential) willing to use a highly effective method of contraception in addition to a condom (see Section 10.6.1), if applicable (unless anatomically sterile or where abstaining from sexual intercourse is in line with the preferred and usual lifestyle of the participant) from first dose until 4 months after last dose of IMP.
3. Participant with a body mass index (BMI) of 18-30kg/$m^2$. (Inclusive)
   BMI = body weight (kg) / [height (m)]$^2$.
4. No clinically significant history of previous allergy / sensitivity to AX-158 or any of the excipients contained within the IMP.
5. Participant with no history of autoimmune disease, cardiac disease, kidney disease or any food intolerance.
6. No clinically significant abnormal test results for serum biochemistry, haematology and/or urine analyses within 28 days before the first dose administration of the IMP.
7. Total serum bilirubin, alkaline phosphatase (ALP), aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 1.5 x upper limit of normal (ULN). If total bilirubin is above the upper limit of normal and is then fractionated, direct bilirubin must be within normal limits.
8. Total serum Testosterone levels 2 x above the lower limit of the normal range within 28 days before the first dose administration of the IMP.
9. Participant with a negative urinary drugs of abuse (DOA) screen (including alcohol) test results, determined within 28 days before the first dose administration of the IMP (N.B.: A positive test result may be repeated at the Investigator's discretion).
10. Participant with negative human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg)) and hepatitis C virus antibody (HCV Ab) test results at Screening.
11. No clinically significant abnormalities in 12-lead electrocardiogram (ECG) determined within 28 days before first dose of IMP including a QRS > 120ms, PR interval > 220ms and QT interval corrected using Fredericia's formula (QTcF) > 450ms.
12. No clinically significant abnormalities in vital signs (e.g., blood pressure/heart rate, respiration rate and oral temperature) determined within 28 days before first dose of IMP.
13. Participant must be available to complete the study (including all follow-up visits).
14. Participant must satisfy an Investigator about his fitness to participate in the study.
15. Participant must provide written informed consent to participate in the study.
16. Participants with a negative COVID-19 test on admission.

17. Participants who are considered fully vaccinated to COVID-19 as per the current Welsh/UK Government guidelines.

**To be re-confirmed on Day -1 / prior to first dose administration:**

1. Participant continues to meet all screening inclusion criteria.
2. Participant with a negative urinary DOA screen (including alcohol) prior to first dose administration.
3. Participants with a negative COVID-19 test on admission (if required).

### 10.5.2 Exclusion Criteria

**To be confirmed at Screening:**

1. A clinically significant history of gastrointestinal disorder likely to influence IMP absorption.
2. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 28 days or 5 half-lives (whichever is longer) prior to the first dose of IMP. Occasional use of paracetamol will be allowed
3. Evidence of renal, hepatic, central nervous system, respiratory, cardiovascular, or metabolic dysfunction.
4. A clinically significant history of drug or alcohol abuse (defined as the consumption of more than 14 units [for male and female participants] of alcohol a week) within the past two years.
5. Inability to communicate well with the Investigators (i.e., language problem, poor mental development, or impaired cerebral function).
6. Participation in a New Chemical Entity (NCE) clinical study within the previous 3 months or five half-lives, whichever is longer, or a marketed drug clinical study within the 30 days or five half-lives, whichever is longer, before the first dose of IMP. *(Washout period between studies is defined as the period of time elapsed between the last dose of the previous study and the first dose of the next study).*
7. Donation of 450 mL or more blood within the 3 months before the first dose of IMP.
8. Vegans, vegetarians, or other dietary restrictions (e.g., restrictions for medical, religious, or cultural reasons, etc), which would prevent participants from consuming a high-fat breakfast or standardised meal.
9. Users of nicotine products i.e., current smokers or ex-smokers who have smoked within the 6 months prior to screening or users of cigarette replacements (i.e., e-cigarettes, nicotine patches or gums).
10. Participants who have received a COVID-19 vaccine injection within 28 days prior to the first dose of IMP.

**To be re-confirmed at Day -1 / prior to first dose administration:**

1. Development of any exclusion criteria since the Screening visit.
2. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements since Screening.
3. Participation in a clinical study since the Screening visit.
4. Donation of 450 mL or more blood since the Screening visit.

## 10.6 Additional Advice and Restrictions for Study Population

### 10.6.1 Contraception

To prevent pregnancy, male participants (and partner of childbearing potential) must be willing to use a highly effective method of contraception in addition to a condom, if applicable (unless partner is of non-childbearing potential or where abstaining from sexual intercourse was in-line with the preferred and usual lifestyle of the participant [periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception]) from the first dose until 4 months after the last dose.

Highly effective methods of contraception include:

- Combined (oestrogen and progestogen containing) hormonal contraception (oral, intravaginal, and transdermal) associated with inhibition of ovulation,
- Progestogen-only hormonal contraception (oral, injectable, and implantable) associated with inhibition of ovulation,
- Intrauterine device (IUD),
- Intrauterine hormone-releasing system (IUS),
- Bilateral tubal occlusion,
- Vasectomised participant (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate. In the absence of such documentation, condoms will be required).

To prevent exposure of any partner (male or female) during non-vaginal intercourse to the semen from a male participant who has been exposed to the IMP, the following contraception must be used:

- Condom.

The chosen contraception method(s) must be followed from the first dose until at least 4 months after receiving the last dose of IMP.

In addition, male participants must use a condom when engaging in sexual intercourse with a female who is pregnant or breastfeeding during the study.

### 10.6.2 Sperm Donation

Participants must not donate sperm from the first dose and for at least 4 months after the last dose of IMP.

### 10.6.3 Phototoxicity

Data on the potential phototoxicity of AX-158 is not yet available. Participants should therefore avoid exposure to direct sunlight from the first dose and should remain within the Phase I unit until 24 hours after the (last) dose.

### 10.6.4 Diet and Fluid Restrictions

### 10.6.5 Meal Times/Fasts

Participants should receive standardised meals (as determined by the clinical unit) scheduled at the same time for all participants in each cohort (relative to their dosing time).

Participants will fast overnight for at least 10 h then -

Lunch will be served: approximately 4 h post-dose.

Dinner will be served: approximately 8 h post-dose.

Snack will be served: approximately 12 h post-dose.

Participants are required to fast for at least 8 h prior to laboratory sample collection for the following tests:

For blood glucose tests (analysed in serum or plasma).

Please refer to Table 10.9.1, Table 10.9.2 and Table 10.9.3. for scheduling of these tests.

On all non-dosing study days, whilst resident in the Clinical Unit, meals will be served at standard times.

Participants will choose meals from a standard menu while resident at the Clinical Unit.

**Part B Food-Effect:**

Participants will fast overnight for at least 10 h then –

During the fed treatment period, participants will be provided with a high fat breakfast** to be consumed within 30 mins or less. The study drug should be administered approximately 30 min after the start of the meal.

**A high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal is recommended as a test meal for food-effect bioavailability and fed bioequivalence studies. This test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively. An example test meal consists of two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes and eight ounces of whole milk[5].

If it is determined following review of the Food Effect Cohort data that all cohorts in Part C should be administered AX-158 in the fed state, the meal will comprise of a standardised meal as per the standard for the Clinical Unit.

### 10.6.6 Fluid Intake

No fluids (apart from water taken with the dose) are allowed from 1 h prior to dosing until 1 h afterwards. Water is then allowed *ad libitum* and at least 240 mL should be consumed every 4 h during waking hours. Squash/cordial/hot drinks (decaffeinated tea and coffee) are allowed from 4 h post-dose.

### 10.6.7 Alcohol Intake

The consumption of alcohol will be limited to a maximum of 2 units per day from 7 days prior to the first dose of IMP. Alcohol will be avoided completely for a period of not less than 2 days prior to the first dose of IMP and throughout the study period. Any deviation outside this alcohol intake restriction will be assessed on a case-by-case basis at the Investigator's discretion (provided the participant's alcohol intake will not impact in the safety aspects and objectives of the study and the participant has a negative alcohol screen prior to dosing).

### 10.6.8 Caffeine

Food or drink containing caffeine, including coffee, tea, cola, energy drinks or chocolates will be avoided completely 2 days prior to dosing and whilst the participants are resident in the Clinical Unit (during each dosing period).

### 10.6.9 Poppy and Sesame Seeds

Participants will be advised that they must not eat food containing poppy and/or sesame seeds for 3 days before each visit to the Clinical Unit, as consumption of poppy and/or sesame seeds can lead to a positive opiate result in the drugs of abuse test.

### 10.6.10 Grapefruit Juice and Other Restrictions

No food or drink containing grapefruit, cranberry, or Seville oranges (including marmalade and fruit juices), and/or food or drink, sweets, candies, or other confectionary containing liquorice will be allowed from 7 days before the first dose of IMP until the final study visit.

## 10.7 Other Life-Style Restrictions

### 10.7.1 Strenuous Exercise

Strenuous exercise must be avoided completely from 3 days before the first dose of IMP until the final study visit.

### 10.7.2 Blood Donation

Participants will be advised that they should not donate blood for at least 3 months after the final study visit.

### 10.7.3 Exposure to Sunlight

Participants should avoid exposure to direct sunlight from the first dose until 24 h after the (last) dose.

### 10.7.4 Removal of Participants from Therapy or Assessment

Each participant will be informed of their right to withdraw from the study at any time and for any reason.

An Investigator will withdraw a participant from the study at any time for any of the following reasons:

- If a participant experiences a serious or intolerable AE, that prevents them from continuing.
- If a participant incurs a significant protocol violation which impacts on their safety or the scientific integrity of the study (this will be discussed on a case-by-case basis with the sponsor).
- At the request of the Sponsor.
- If it is considered that the participant's health is compromised by remaining in the study or the participant is not sufficiently cooperative.
- If a participant is lost to follow-up.

The reasons for any participant withdrawal will be recorded on the study completion form of the electronic case report form (eCRF).

If a participant is withdrawn or chooses to withdraw from the study for any reason every possible effort will be made to perform the evaluations described for the post-study follow-up (see Table 10.9.1, Table 10.9.2 and Table 10.9.3). The data collected from withdrawn participants will be included in the study report.

In the event of any abnormalities considered to be clinically significant, participants will be followed-up with appropriate medical management until values are considered to be clinically acceptable. Referral or collaborative care will be organised if considered necessary.

Up to one hundred and four (104) participants are planned to be enrolled into the study. Participants who withdraw from the study before receiving any IMP will be replaced. Participants who are withdrawn from the study due to significant drug-related AEs will not be replaced. Replacement of all other participants withdrawn from the study after receiving IMP will be decided on a case-by-case basis by the Principal Investigator (or deputy) and Sponsor.

## 10.8 Investigational Medicinal Product

### 10.8.1 Identity

The identity of each IMP is detailed in Table 10.8.1 Identity of Investigational Medicinal Products.

**Table 10.8.1 Identity of Investigational Medicinal Products**

| IMP Name | Strength | Presentation/Form | Route |
|---|---|---|---|
| AX-158 | Minimum of 5 mg API per capsule | Capsule | Oral |
| Matching Placebo (per capsule strength) | N/A | Capsule | Oral |

### 10.8.2 Receipt and Storage

The active pharmaceutical ingredient (API) (AX-158) will be supplied by the Sponsor.

The Sponsor must notify the Principal Investigator, or the Project Manager, prior to dispatch of supplies, and of the anticipated date of their arrival. API should arrive at the study site at least 4 weeks before the first dosing day. The Sponsor shall address all supplies to:

The Production Manager

IMP Management
Simbec-Orion
Merthyr Tydfil Industrial Park
Merthyr Tydfil CF48 4DR

Upon receipt, supplies will be dealt with as per Simbec-Orion SOPs. Temperature monitors included with shipments will be downloaded.

The API will be stored under quarantine, at 15-25ºC in a secure, temperature-controlled GMP area. A sample will be taken and sent to Simbec-Orion's contract laboratory to confirm identity. A Simbec-Orion Qualified Person (QP) will review the shipping documentation and certificate of analysis. The supplies will subsequently be removed from quarantine and approved for use.

### 10.8.3 Assembly and Release

The IMP will be assembled into unit doses by suitably trained Simbec-Orion staff according to Simbec-Orion SOPs.

The IMP will be labelled as specified in Annex 13 (manufacture of IMPs) of the European Commission (EC) guide to Good Manufacturing Practice (GMP)[6].

The finished IMP will be certified by a Simbec-Orion QP and stored in a secure, temperature-controlled GMP area according to Simbec-Orion SOPs .

### 10.8.4 Administration

**Part A**

The following IMPs will be administered:

- AX-158 capsules
- Matching placebo

The IMPs will be administered fasted (after an overnight fast of at least 10 h) with 240 mL water. More water may be provided (except on PK days) if needed and the actual water taken

with dose administration will be recorded in the eCRF. Participants must remain in a sitting position for at least 1 h after dose.

**Part B**
Each participant will receive the following IMP over 2 treatment periods (1/period) in accordance with the randomisation code:

- AX-158 capsules

The IMP will be administered in either the fed or fasted (after an overnight fast of at least 10h or following consumption of a high-fat breakfast) state in accordance with the randomisation with 240 mL of water. More water may be provided (except on PK days) if needed and the actual water taken with dose administration will be recorded in the eCRF. There will be at least 7 days between doses.

**Part C**

The following IMPs will be administered:

- AX-158 capsules
- Matching placebo

The IMPs will be administered fasted (after an overnight fast of at least 10 h) with 240 mL water. More water may be provided (except on PK days) if needed and the actual water taken with dose administration will be recorded in the eCRF. Participants must remain in a sitting position for at least 1 h after dose. If food effect is seen, cohorts in Part C could be dosed with a standardised meal (as opposed to the high-fat breakfast).

For Part A (SAD) and Part C (MAD), a dose leader design will be implemented with 2 participants being dosed on the first dosing day of each cohort. Of these 2, 1 will be on active drug and 1 on placebo. The remainder of the cohort will be dosed at least 24 h later pending an acceptable safety profile in the dose-leader group and will contain at least 1 additional placebo participant. This design allows maintenance of the "blind".

IMP administration will be documented in the eCRF.

### 10.8.5 Return/Destruction

All used IMP containers and unused IMP will be held under quarantine pending return/destruction.

The Sponsor must provide approval for return/destruction of all remaining IMP within 8 weeks study completion. After this period, a charge for storage will be incurred.

All returns will be arranged at the earliest available delivery date. For IMP destruction, the sponsor will receive the Certificate of Destruction 4 to 6 weeks from the date of removal from site.

### 10.8.6 Method of Assigning Participants to Treatment Groups

Participants will be allocated to treatment groups according to a randomisation code produced by Simbec-Orion using the PROC PLAN procedure of SAS® (the most up to date version will

be used and this will be documented in the Statistical Analysis Plan [SAP]). The randomisation code will include 2 dose-leaders (1 active:1 placebo) in each cohort (for Part A and Part C only).

Participants will be numbered sequentially from 001 (i.e., 001, 002 etc.). Replacement participants will be assigned the same randomisation as the participant they are replacing, however, 100 will be added to the number (i.e., 101 would replace 001 etc.).

### 10.8.7 Selection of Doses in the Study

The starting dose of AX-158 for the FIH study is selected based on FDA (2005) and EMA (2017) guidelines using nonclinical PK and toxicological data.

The NOAEL-based maximum recommended starting dose (MRSD) according to the FDA was calculated using the NOAEL from the rat, which was the most sensitive species.

The NOAEL, as derived from the 28-day toxicology study in rats, was 15 mg/kg/day. The human equivalent dose (HED) was calculated as 15 mg/kg / 6.2 = 2.4 mg/kg. Applying a standard safety factor of 10 (per FDA guidance), and a standard body weight of 60 kg, the NOAEL based maximum recommended starting dose (MRSD) would be (2.4 x 60)/10 = **14.4 mg**.

The efficacious dose in a murine EAE model treated for 23 days is 1 mg/kg. This dose corresponds to 0.69 µg/mL and 0.942 µg.h/mL $C_{max}$ and $AUC_{last,}$ respectively. The MED dose in mouse at 1 mg/kg corresponds to a target AUCu= 942*0.27= 254 ng*h/mL. Assuming a 0.22 unbound fraction for humans, this would correspond to a human AUC of 1150 ng*h/mL as per human efficacious dose projection modelling[1].

A dose of 15 mg AX-158 dosed QD would result in exposure in a range similar to mouse AUC at 1 mg/kg[1]. Nonetheless, a starting dose 3x below the projected efficacious dose in humans is proposed and therefore 5 mg is suggested as the starting dose in humans. This approach meets the EMA *Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products, 2018* which states that the starting dose should be a dose expected to result in an exposure lower than pharmacology active dose.

As this is a first-in-human study, it is acknowledged that only the selected starting dose for the first cohort (5 mg) in the Single Ascending Dose (SAD) part of the study (Part A) is fixed; all other dose levels to be evaluated in subsequent cohorts with Part A are subject to selection following dose escalation data review of PK and safety data from the previous cohorts. However, the anticipated doses for evaluation in the 5 cohorts of Part A of the study are as shown in Table 10.8.2 below,.

The table summarises two scenarios where i) at least 3 of the proposed dose levels are expected to be above the efficacious exposure according to PK modelling and ii) all dose levels would be in the therapeutic range according to BSA conversion factors.

**Table 10.8.2 Summary of predicted human exposures and multiples of the HED**

| Human Phase I Proposed Dose Levels (mg) | PK Modelling Human exposure vs Mouse MED (AUCs ug.h/ml) * | BSA conversion Human Phase I (mg/kg) ** | Multiples of HED (0.083 mg/kg) from the EAE model (BSA basis) |
|---|---|---|---|
| **5** | 0.38 | **0.083** | **1** |
| **10** | 0.77 | **0.167** | **2** |
| **15** | **1.17** | **0.25** | **3** |
| **25** | **1.87** | **0.42** | **5** |
| **40** | **3.04** | **0.67** | **8** |

*Efficacious exposure 0.942 µg.h/mL. Values based on CERTARA projections **Assuming a 60 kg average body weight. Dose levels expected to be within the therapeutic range based on both approaches are identified in bold and red.

On the basis of the above table and a maximum proposed dose of 40 mg, it is anticipated that the maximum dose will fall within the estimated human pharmacodynamic dose range. Efficacy on the EAE model has been confirmed both at 1 and 10 mg/kg in mice which would correlate on a BSA basis to 5 and 50 mg in humans. Accordingly, it is considered that the planned doses up to and including the maximum planned dose will all fall under the estimated pharmacodynamic dose range.

As detailed within Section 10.2, the proposed dose levels may be adapted and modified if the actual human exposure levels (evaluated following cohort dose escalation data review) are below the levels predicted by the PK modelling. This additional measure guarantees that the study includes representative dose levels within the pharmacodynamic range. If a higher dose than the proposed maximum dose of 40 mg is to be evaluated (following dose escalation data review), an estimation of AX-158 exposure will be performed in order to determine that this higher dose will not exceed the exposure limits as set within the protocol pre-defined stopping criteria (Cmax= 3.26 ug/mL; AUC= 14.859 µg.h/mL) or exceed the estimated human pharmacodynamic dose range. If it is determined that this higher dose will indeed exceed the exposure limits or exceed the estimated human pharmacodynamic dose range, an appropriate substantial amendment will be submitted for review and approval by the REC and MHRA and dosing will only proceed following receipt of approval of this substantial amendment.

AX-158 will be given as a flat dose at each dose level, based on a 60 Kg volunteer. Eligible participants will be enrolled in sequential cohorts treated with AX-158, given as an oral capsule dose while being monitored for safety.

### 10.8.8 Dose Range to be Investigated

Part A (SAD): No dose level that is predicted to exceed either the $C_{max}$ or $AUC_{0-24}$ seen at the NOAEL in the nonclinical studies will be administered in this study without prior approval, via substantial amendment, from REC and MHRA. During the study, PK data from the previous cohort/s, along with safety and tolerability information, will be used to aid dose selection and the magnitude of the dose increase for the next cohort.

Part B (Food effect): The dose level at which the food effect will be performed will be based on a review of all available safety and PK data from Part A and will not exceed a dose tolerated in Part A.

Part C (MAD): The starting dose in Part C will not be expected to exceed the highest established AX-158 exposure ($C_{max}$ and $AUC_{0-24}$) from Part A. Doses of AX-158 and matching placebo for Part C will be selected based on safety, tolerability and pharmacokinetic considerations from Part A (and where applicable previous cohort/s of Part C) which will be used to aid dose selection, magnitude of the dose increase for the next cohort and review of dosing regimen if appropriate. The maximum dose administered in a 24 h period will not exceed a level anticipated to result in a $C_{max}$ or $AUC_{0-24}$ exceeding those observed at NOAEL levels in nonclinical species without prior approval by the REC and MHRA (via substantial amendment).

### 10.8.9 Dose Escalation Increments

The planned dose escalation for all cohorts (with the exception of Part A [SAD] Cohort 1) is up to a 2-fold increase of the previous dose level. In Part A, it is planned to investigate up to 5 dose levels; however, it is possible that 2 additional dose level(s) may be investigated if justified based on available safety, tolerability, and PK data. In Part C, it is planned to investigate up to 3 dose levels; however, it is possible that 2 additional dose level(s) may be investigated if justified based on available safety and PK data. Dose escalation increments may vary from those planned but will not exceed 2-fold; the Sponsor and the Principal Investigator may decide not to proceed with further dose cohorts, to administer a lower or intermediate dose, to repeat a dose in subsequent cohorts or to proceed to a higher dose if at all. A dose level will not be repeated if dose escalation stopping criteria have been met at that dose level. It is noted that escalation/continuation to the next dose level will not occur if any individual participant's $C_{max}$ or $AUC_{0-24}$ data exceeds those levels seen at the NOAEL in the most sensitive preclinical species, (AX-158 $C_{max}$ of 3.26 ug/mL and AUC of 14.859 µg*h/mL(males), or if they are anticipated to do so at the next dose level based on emerging PK data.

### 10.8.10Timing of Dose for Each Participant

Participants will be required to fast for at least 10 h overnight prior to each morning dose. The fast will be broken 4 h after dosing with a light lunch (see Section 10.6.5). If the study is to be performed during fed conditions, it is recommended that participants should start the meal 30 minutes prior to administration of the drug product and eat this meal within 30 minutes. The caloric breakdown of the test meal should be provided in the study protocol, Section 10.6.5.

For Part A (SAD) and Part C (MAD) two (2) dose leaders (1 active:1 placebo) will be dosed first in each cohort. The remainder of the cohort will be dosed at least 24 h later pending an acceptable safety profile in the dose-leader group.

### 10.8.11Blinding

A designated individual from the IMP Management Department at Simbec-Orion will generate the randomisation code under the guidance of a statistician. All other site and Sponsor personnel involved in the study will be blinded with regards to the IMP being administered. The team responsible for the preparation of participant doses and emergency code break

envelopes will not be blinded and a copy of the original randomisation code will be issued to them for this purpose.

The Simbec-Orion Bioanalytical Scientist will be provided with a copy of the randomisation code for the purposes of analysing samples. The Bioanalytical Scientist will provide the drug concentration data for interim analysis and dose escalation data review in a re-coded participant number format, presented by dose level, in order to maintain the blind of study personnel.

The Simbec-Orion Pharmacology team members will be provided with a copy of the randomisation code for the purposes of PK analysis.

**Participant doses:** Once the randomisation code has been authorised as per Simbec-Orion SOPs, each participant dose will be packaged and labelled for individual participants by designated individuals from the IMP Management Department at Simbec-Orion on behalf of the Sponsor. The QP checks that the active drug and placebo are indistinguishable as part of the QP certification process.

**Code break envelopes:** Once the randomisation code has been authorised as per Simbec-Orion SOPs, the IMP Management team will produce individual sealed code-break envelopes that contain the treatment allocation(s) for each participant. The envelopes will be stored in a restricted access area. A set of code break envelopes will also be provided to the Simbec-Orion Pharmacovigilance (PV) Department.

*Emergency unblinding:* Where the site requires emergency access to an individual participant code Simbec-Orion will break the blind via the code break envelopes without prior consultation with the Sponsor. In such an event, the Sponsor will be notified as soon as possible via email.

*Non-emergency unblinding:* If an Investigator believes that knowledge of the IMPs received by a participant is essential for appropriate treatment of an AE, the code will be broken via the code break envelopes. Where practical, the Investigator should ideally consult the Sponsor before breaking the code. In any event, the Sponsor will be informed as soon as practical whenever the code has been broken for a participant.

If the blind needs to be broken for an individual participant, the date and reason will be recorded in the participant's eCRF. The Investigator will not reveal the unblinded treatment code to any other member of the clinical team involved in the study or to the Study Monitor. If the code is broken for any individual participant, the participant will be withdrawn from the study and the procedures accompanying withdrawal performed. If the code is broken without justification, this will be deemed a serious protocol deviation.

### 10.8.12 Prior and Concomitant Therapy

**Prior Medication:** Prescription or non-prescription drugs, including vitamins, herbal and dietary supplements should not be taken within 28 days (or 5 half-lives (whichever is longer)) prior to the first dose of IMP, unless in the opinion of the Investigator and Sponsor's Responsible Physician the medication will not interfere with the study procedures or compromise participant safety. Prescription or non-prescription drugs, including vitamins, herbal and dietary supplements taken during the 28 days before the first dose of IMP, and the reason for taking them, will be noted in the participant's eCRF.

Participants should not receive a COVID-19 vaccine within 28 days prior to the first dose of IMP.

Inclusion of participants who have taken prior medication will be reviewed on a case-by-case basis in relation to the safety aspects and objectives of this study.

**Concomitant Medication:** Prescription or non-prescription drugs, including vitamins, herbal and dietary supplements should not be taken throughout the duration of the study, with the exception of paracetamol (which may be taken as an analgesic to a maximum of 2g in 24 h).

Participants should not receive a COVID-19 vaccine from the first dose of IMP to completion of the post-study follow up visit.

If intake of any prior or concomitant medication is necessary during the study, the daily dosage, duration, and reasons for administration will be recorded on the participant's eCRF.

#### 10.8.13Treatment Compliance

Each dose of IMP will be taken under supervision and a hand and mouth check conducted. The exact dosing time for each participant will be recorded on the participant's eCRF.

## 10.9 Efficacy and Safety Variables

### 10.9.1 Efficacy and Safety Measurements Assessed and Flow Chart

A schedule of study assessments is provided in in Table 10.9.1, Table 10.9.2 and Table 10.9.3

Simbec-Orion personnel who have been appropriately trained will carry out study procedures.

Where more than 1 procedure is scheduled for the same time-point, the following order of priority will apply:

1. PK blood sampling. Blood samples collected outside of the defined deviation windows will be recorded as protocol deviations: ± 1 minute for samples collected up to 45 minutes time-point (inclusive) and ± 5 minutes for samples collected > 45 minutes time-point.
2. Vital signs and 12-lead ECG (a window of ± 10 min in relation to the nominal time-point is allowed).
3. Start or finish of urine collection interval (a window of ± 10 min in relation to the nominal time-point).

All baseline assessments may be performed within the 1 h before dosing.

## Table 10.9.1 Study Flow Chart – Part A Single Ascending Dose

| Visits[1,2] | Screening | Treatment Period | | | | | | | | | | | | | | | Follow up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | In-house | | | | | | | | | | | | | | | |
| **Days** | **Day – 28 to -2** | **Day - 1** | **Day 1** | | | | | | | | | | | **Post-Treatment 1 (Day 2)** | | **Post-Treatment 2 (Day 3)** | **Post-Treatment 3 (Day 4)** | **5-7 days from last IMP dose** |
| **Time (h)** | | | **Pre-Dose** | **0** | **0.5** | **0.75** | **1h** | **2h** | **3h** | **4h** | **6h** | **8h** | **12h** | **24h** | **36h** | **48h** | **72h** | |
| Informed Consent | X | | | | | | | | | | | | | | | | | |
| Inclusion/Exclusion[3] | X | X | X | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | |
| Height/Weight/BMI[4] | X | X | | | | | | | | | | | | | | | | |
| Medical History & Concurrent Conditions | X | | | | | | | | | | | | | | | | | |
| Virology Tests (HIV, HBsAg, HCV) | X | | | | | | | | | | | | | | | | | |
| Drug and Alcohol Screen[5] | X | X | | | | | | | | | | | | | | | | |
| COVID-19 Test | | X | | | | | | | | | | | | | | | | |
| Biochemistry | X[6] | X | | | | | | | | | | | | X | | | X | X |
| Haematology | X | X | | | | | | | | | | | | X | | | X | X |
| Urinalysis | X | X | | | | | | | | | | | X | X | | | X | X |
| Coagulation[7] | X | X | | | | | | | | | | | | X | | | X | X |
| Randomisation | | | X | | | | | | | | | | | | | | | |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Vital Signs[8] | X | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical Examination | X | X[11] | | | | | | | | | | | | | | | X[11] | X[11] |
| 12-Lead ECG[9] | X | X | X | | X | | | | | X | | | X | X | | X | X | X |

| Visits[1,2] | Screening | Treatment Period | | | | | | | | | | | | | | | Follow up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | In-house | | | | | | | | | | | | | | | |
| **Days** | **Day – 28 to -2** | **Day - 1** | **Day 1** | | | | | | | | | | | **Post-Treatment 1 (Day 2)** | | **Post-Treatment 2 (Day 3)** | **Post-Treatment 3 (Day 4)** | **5-7 days from last IMP dose** |
| **Time (h)** | | | **Pre-Dose** | **0** | **0.5** | **0.75** | **1h** | **2h** | **3h** | **4h** | **6h** | **8h** | **12h** | **24h** | **36h** | **48h** | **72h** | |
| Prior & Concomitant Medication | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Dose IMP[10] | | | | X | | | | | | | | | | | | | | |
| Blood Sampling for PK | | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Exploratory PD sample | | | X[12] | | | | | | | | | | | | | | | |

| **Study Flow Chart Footnotes:** | |
|---|---|
| **1** | All cohorts will complete only 1 Treatment Period. |
| **2** | Participants will be in the clinical unit for their in-house period from the morning before dosing (Day -1), until the completion of all the assessments on Post-Treatment 3 (Day 4). |
| **3** | Eligibility will be determined during screening. Continued eligibility will be confirmed on Day -1, and pre-dose Day 1. |
| **4** | Height measured at Screening only. |
| **5** | A urine sample will be used to screen for drugs of abuse (including alcohol and cotinine). |
| **6** | Total serum testosterone only required at screening. |
| **7** | Coagulation testing aPTT and PT |
| **8** | Vital signs include the following assessments: supine systolic and diastolic blood pressure, supine heart rate, respiration rate and oral temperature |
| **9** | 12-lead ECG will be performed at screening, each period pre-dose and at 30 min, 4 h, 12 h, 24 h, 48 h and 72 h post-dose and at the post-study follow up visit. |
| **10** | IMP or placebo will be administered orally in a fasted state (after an overnight fast of at least 10 h) with 240 mL water. The fast will be broken 4 h post-dose with lunch. |
| **11** | Symptom directed |
| **12** | Cohort 3 onwards additional samples will be taken based on emerging data |

## Table 10.9.2 Study Flow Chart – Part B Food Effect

| Visits[1,2] | Screening | Treatment Periods 1 & 2 | | | | | | | | | | | | | | | | Follow up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | In-house | | | | | | | | | | | | | | | | |
| Days | Day – 28 to -2 | Day - 1 | Day 1 | | | | | | | | | | | Post-Treatment 1 (Day 2) | | Post-Treatment 2 (Day 3) | Post-Treatment 3 (Day 4) | 5-7 days from last IMP dose |
| Time (h) | | | Pre-Dose | 0 | 0.5 | 0.75 | 1h | 2h | 3h | 4h | 6h | 8h | 12h | 24h | 36h | 48h | 72h | |
| Informed Consent | X | | | | | | | | | | | | | | | | | |
| Inclusion/Exclusion[3] | X | X | X | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | |
| Height/Weight/BMI[4] | X | X | | | | | | | | | | | | | | | | |
| Medical History & Concurrent Conditions | X | | | | | | | | | | | | | | | | | |
| Virology Tests (HIV, HBsAg, HCV) | X | | | | | | | | | | | | | | | | | |
| Drug and Alcohol Screen[5] | X | X | | | | | | | | | | | | | | | | |
| COVID-19 Test | | X | | | | | | | | | | | | | | | | |
| Biochemistry | X[6] | X | | | | | | | | | | | | X | | | X | X |
| Haematology | X | X | | | | | | | | | | | | X | | | X | X |
| Urinalysis | X | X | | | | | | | | | | | X | X | | | X | X |
| Coagulation[7] | X | X | | | | | | | | | | | | X | | | X | X |
| Randomisation | | | X | | | | | | | | | | | | | | | |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Vital Signs[8] | X | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical Examination | X | X[11] | | | | | | | | | | | | | | | X[11] | X[11] |
| 12-Lead ECG[9] | X | X | X | | X | | | | | X | | | X | X | | X | X | X |
| Prior & Concomitant Medication | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Dose IMP[10] | | | | X | | | | | | | | | | | | | | |

| Visits[1,2] | Screening | Treatment Periods 1 & 2 | | | | | | | | | | | | | | | | Follow up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | In-house | | | | | | | | | | | | | | | | |
| **Days** | **Day – 28 to -2** | **Day - 1** | **Day 1** | | | | | | | | | | | **Post-Treatment 1 (Day 2)** | | **Post-Treatment 2 (Day 3)** | **Post-Treatment 3 (Day 4)** | **5-7 days from last IMP dose** |
| **Time (h)** | | | **Pre-Dose** | **0** | **0.5** | **0.75** | **1h** | **2h** | **3h** | **4h** | **6h** | **8h** | **12h** | **24h** | **36h** | **48h** | **72h** | |
| Blood Sampling for PK | | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | |

| **Study Flow Chart Footnotes:** | |
|---|---|
| **1** | All cohorts will complete Treatment Period 1 & 2. |
| **2** | For Treatment Periods 1 & 2, participants will be in the clinical unit for their in-house period from the morning before dosing (Day -1), until the completion of all the assessments on Post-Treatment 3 (Day 4). |
| **3** | Eligibility will be determined during screening. Continued eligibility will be confirmed on Day -1, and pre-dose Day 1 for Treatment Periods 1 & 2. |
| **4** | Height measured at Screening only. |
| **5** | A urine sample will be used to screen for drugs of abuse (including alcohol and cotinine). |
| **6** | Total serum testosterone only required at screening. |
| **7** | Coagulation testing aPTT and PT |
| **8** | Vital signs include the following assessments: supine systolic and diastolic blood pressure, supine heart rate, respiration rate and oral temperature |
| **9** | 12-lead ECG will be performed at screening, each period pre-dose and at 30 min, 4 h, 12 h, 24 h, 48 h and 72 h post-dose and at the post-study follow up visit. |
| **10** | Participants will receive a single dose of AX-158 following an overnight fast of at least 10 h OR following consumption of a high-fat breakfast over 2 treatment periods (1 per period). AX-158 should be administered 30 mins after the start of the meal. |
| **11** | Symptom directed |

## Table 10.9.3 Study Flow Chart – Part C Multiple Ascending Dose

| **Visits[1]** | **Screening** | **In-house** | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Days** | **Day – 28 to -2** | **Day - 1** | **Day 1-4, Day 10-13[15]** | | | | | | | | | | | | | | | **Day 5-9** | **5-7 days from last IMP dose** |
| **Time (h)** | | | **Pre-Dose** | **0** | **0.5** | **0.75** | **1h** | **2h** | **3h** | **4h** | **6h** | **8h** | **12h** | **24h** | **36h** | **48h** | **72h** | | |
| Informed Consent | X | | | | | | | | | | | | | | | | | | |
| Inclusion/Exclusion[2] | X | X | X | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | | |
| Height/Weight/BMI[3] | X | X | | | | | | | | | | | | | | | | | |
| Medical History & Concurrent Conditions | X | | | | | | | | | | | | | | | | | | |
| Virology Tests (HIV, HBsAg, HCV) | X | | | | | | | | | | | | | | | | | | |
| Drug and Alcohol Screen[4] | X | X | | | | | | | | | | | | | | | | | |
| COVID-19 Test | | X | | | | | | | | | | | | | | | | X[15] | |
| Biochemistry | X[7] | X[7,8] | | | | | | | | | | | | X[7,8] | | | X | X[6] | X |
| Haematology | X | X | | | | | | | | | | | | X | | | X | X[6] | X |
| Urinalysis | X | X | | | | | | | | | | | X | X | | | X | X[6] | X |
| Coagulation[5] | X | X | | | | | | | | | | | | X | | | X | X[6] | X |
| Randomisation | | | X | | | | | | | | | | | | | | | | |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Vital Signs[9] | X | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X[6] | X |
| Physical Examination | X | X[13] | | | | | | | | | | | | | | | X[13] | | X[13] |
| 12-Lead ECG[10] | X | X | X | | X | | | | | X | | | X | X | | X | X | X[6] | X |
| Prior and Concomitant Medication | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Dose IMP[11] | | | | X | | | | | | | | | | X | | X | X | X | |
| Blood Sampling for PK | | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X[14] | |

| **Visits**[1] | **Screening** | **In-house** | | | | | | | | | | | | | | | | **Follow up** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Days** | **Day – 28 to -2** | **Day - 1** | **Day 1-4, Day 10-13**[15] | | | | | | | | | | | | | | **Day 5-9** | **5-7 days from last IMP dose** |
| **Time (h)** | | | **Pre-Dose** | **0** | **0.5** | **0.75** | **1h** | **2h** | **3h** | **4h** | **6h** | **8h** | **12h** | **24h** | **36h** | **48h** | **72h** | | |
| Urine Sampling for PK | | | X[12] | ← | | | | | | | | | | | | | → | |
| Exploratory PD sample | | | X[16] | | | | | | | | | | | | | | | |

| **Study Flow Chart Footnotes:** | |
|---|---|
| **1** | For each cohort participants will be in the clinical unit for their inpatient visit from the morning before dosing (Day -1), until the completion of all assessments on Day 13. |
| **2** | Eligibility will be determined during screening. Continued eligibility will be confirmed on Day -1, and pre-dose Day 1- 10 |
| **3** | Height measured at Screening only. |
| **4** | A urine sample will be used to screen for drugs of abuse (including alcohol and cotinine). |
| **5** | Coagulation testing aPTT and PT |
| **6** | Pre dose on Day 7 only |
| **7** | Total serum testosterone required at screening, pre dose D-1 and on D11 |
| **8** | Serum LH required at pre dose (D-1) and on D11 |
| **9** | Vital signs include the following assessments: supine systolic and diastolic blood pressure, supine heart rate, respiration rate and oral temperature |
| **10** | 12-lead ECG will be performed at screening, pre-dose and at 30 min, 4 h, 12 h, 24 h, 48 h and 72 h post-dose Days 1 and 10 and at the post-study follow up visit. |
| **11** | For all cohorts IMP or placebo will be administered orally in a fasted state (after an overnight fast of at least 10 h) with 240 mL water. The fast will be broken 4 h post-dose with lunch on Days 1-10. |
| **12** | Urine sampling: for AX-158: pre-dose and in intervals of 0-12, 12-24, 24-48 and 48-72 h post-dose on Day 1 and Day 10 |
| **13** | Symptom Directed |
| **14** | Pre-dose trough sample day 5 only |
| **15** | COVID-19 test on day 8 and prior to check out. |
| **16** | Additional samples will be taken based on emerging data |

### 10.9.2 Demographic and Background Assessments

The following demographic and background assessments will be performed during the study at the time-points specified in in Table 10.9.1, Table 10.9.2 and Table 10.9.3

### 10.9.3 Demographics

Demographic data: age, year of birth, gender, race, ethnicity, height, weight, and BMI.

Height in metres (to the nearest cm) and weight in kg (to the nearest 0.1 kg) in indoor clothing and without shoes will be measured. BMI = body weight (kg)/[height (m)]$^2$ will be calculated.

### 10.9.4 Medical History and Concurrent Conditions

Relevant medical history and current conditions will be recorded in the eCRF.

### 10.9.5 Virology Tests

Virology tests: HBsAg, HCV Ab and HIV test (antibodies to HIV-1 and HIV-2).

Virology tests will be analysed from the same serum sample for biochemistry analyses at Screening by Simbec-Orion Laboratory Services, or at an appropriate referral laboratory, using an appropriate analyser/method(s) of analyses.

### 10.9.6 COVID-19 Testing

A nasopharyngeal and/or oropharyngeal swab will be collected. COVID-19 testing will be routinely performed via lateral flow tests however a RT-PCR test may be performed at the Principal Investigator's discretion by Simbec-Orion Laboratories Services.

### 10.9.7 Drugs of Abuse (including Alcohol and Cotinine)

Urine DOA screen (including alcohol and cotinine): alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids/tetrahydrocannabinoids (THC), cocaine, cotinine, methadone, and opiates.

A **mid-stream** urine sample will be collected into a universal collection/storage container. At protocol-defined time-points when both urinalysis and drugs of abuse/alcohol screening are required, all urine analyses will be performed from a single approximately 20 mL urine sample.

Urine samples for DOA (including alcohol and cotinine) will be analysed by Simbec-Orion Laboratory Services, or at an appropriate referral laboratory, using an appropriate analyser/manual kit(s)/method(s) of analyses.

Assessments of urine sample quality (i.e., urine sample verification/adulteration) will be performed by measuring urine creatinine for urine DOA.

### 10.9.8 Compliance with Inclusion/Exclusion Criteria

An Investigator will assess all participants against the study inclusion and exclusion criteria at Screening. Compliance will be re-confirmed on Day -1/prior to dosing.

### 10.9.9 Efficacy Assessments

Not applicable.

### 10.9.10Safety Assessments

The following safety assessments will be performed at the time-points specified in in Table 10.9.1, Table 10.9.2 and Table 10.9.3

### 10.9.11Adverse Events

AEs and SAEs that occurred during the study along with their severity and relationship to study drug will be reported.

An AE is defined as per SI 2004 No. 1031:

*Any untoward medical occurrence[1] in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.[2]*

Notes:

[1] Whether subjective complaint or objective finding.

[2] An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of an IMP, whether or not considered related to the IMP.

An unexpected adverse reaction is defined as:

*An adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g., IB for an unapproved investigational product of summary of product characteristics (SmPC) for an authorised product).*

AEs will be monitored throughout the study from the signature of participant informed consent through to the post-study follow-up visit. All AEs will be recorded, whether considered minor or serious, drug-related, or not.

All abnormal laboratory findings considered to be clinically significant will be recorded as AEs.

### 10.9.12Recording of Adverse Events

All of the following details will be recorded in the participant's eCRF for each AE:

- Full description of AE.
- Date and time of onset.
- Ongoing (Yes/No)
- End Date and time.
- Severity of event to be assessed by an Investigator in accordance with the definitions below.
- SAE (Yes/No) and seriousness criteria (if applicable)

- Relationship to IMP to be assessed by an Investigator in accordance with the definitions below.
- Action taken (if any).
- Outcome and details of any further follow-up.

### 10.9.13 Grades of Adverse Event Severity

The following grades will be used by an Investigator to describe the severity of AEs.

The following are the only grades, which will be used to describe AE severity. Only 1 severity grade will be used for each AE (e.g., mild - moderate is not acceptable).

| SEVERITY OF THE AE | DEFINITION |
|---|---|
| Mild | The AE does not interfere with the participant's daily routines. It causes no more than slight discomfort or mild objective change in any of the safety parameters assessed during the study as determined by the Investigator. |
| Moderate | The AE interferes with some aspects of the participant's daily routines or moderate objective change in any of the safety parameters assessed during the study as determined by the Investigator. |
| Severe | The AE causes inability to carry out the participant's daily routine or severe objective change in any of the safety parameters assessed during the study as determined by the Investigator. |

### 10.9.14 Definitions of Adverse Event Causality

The following definitions will be used by an Investigator to describe the relationship between an AE and the IMP.

The following are the only definitions which will be used to describe the relationship between AEs and the IMP. Only 1 relationship definition will be used for each AE.

| RELATIONSHIP TO IMP | DEFINITION |
|---|---|
| Reasonable possibility | • There is a reasonable possibility of the event being related to the IMP. This might be temporal or due to a physiological or pharmacodynamic process. |
| No reasonable possibility | • No reasonable possibility of the event being related to the IMP, the IMP may not have been administered, no temporal relationship, and no known or understood physiological or pharmacological mechanism for the event to be related. |

### 10.9.15 Serious Adverse Events

"SAE", "serious adverse reaction" or "unexpected serious adverse reaction" is defined in Statutory Instrument 2004 No. 1031 as any AE, adverse reaction, or unexpected adverse reaction, respectively, that

a. results in death,

Note: Death is an outcome (of an AE, of progressive disease, etc.) and not an AE in itself.

b. is life-threatening,

A life-threatening event places the patient at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

c. requires hospitalisation or prolongation of existing inpatients' hospitalisation,

"In-patient hospitalisation" means that the patient has been formally admitted to a hospital for medical reasons, for any length of time. It does not include presentation to or care within an emergency department.

Complications that occur during hospitalisations are AEs. If a complication prolongs hospitalisation, it is an SAE.

d. results in persistent or significant disability or incapacity, or

e. consists of a congenital anomaly or birth defect.

f. Is otherwise "medically significant" (*e.g.,* that it does not meet preceding criteria, but is considered serious because treatment/intervention would be required to prevent one of the preceding criteria).

Initial or follow-up SAE information must be reported within 24 h of knowledge by submitting an initial or follow-up SAE report via email or fax to Simbec-Orion PV:

E mail: pharmacovigilance@SimbecOrion.com.

SAE Fax: +44 (0)1753 695101; back up SAE Fax: +44 (0)1753 695124.

SAE(s) will be collected throughout the study from the signature of participant informed consent through to the post-study follow-up visit. SAEs occurring after the follow-up period should be reported to the Sponsor if the investigator becomes aware of them.

The SAE Form must be completed as fully as possible with information relevant to the SAE(s) being reported. If it is not possible to complete all sections of the SAE Form within 24 hours, transmission of the form must not be delayed, and the outstanding information should be sent on a follow-up SAE Form.

Simbec-Orion PV will notify the Sponsor and relevant personnel of the SAE via e mail within 1 business day of receipt of the initial SAE report.

AEs which meet all of the following criteria

- Serious.
- Unexpected (i.e., is not consistent with the applicable product information e.g., IB for an unapproved IMP or SmPC for an authorised product).
- There is at least a reasonable possibility that there is a causal relationship between the event and the medicinal product.

will be classified as suspected unexpected serious adverse reactions (SUSARs) and should be reported to the REC and to the MHRA in accordance with applicable regulatory requirements for expedited reporting. Simbec-Orion PV will report SUSARs to the REC and MHRA on behalf of the Sponsor as per the regulatory timeline / It is the Sponsor's responsibility to report SUSARs to the REC and MHRA as per the regulatory timeline.

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the severity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

### 10.9.16 Monitoring of Participants with Adverse Events

In the event of any abnormalities considered to be clinically significant by the investigating physician, participants will be followed up with appropriate medical management until:

- It has resolved/returned to normal or baseline.
- The event has stabilised at a level acceptable to the Investigator and is not considered to be clinically significant.

### 10.9.17 Pregnancy

Pregnancies of female partners of study participants must be reported within 24 h of first knowledge of the PI (or delegate) by submitting a pregnancy notification form via email or fax to Simbec-Orion PV following the same procedures described for SAEs reporting and should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or new-born complications.

Once consent has been obtained, pregnancy outcomes must be collected for the female partners of males who received at least one dose of the IMP on the pregnancy outcome form and should be sent to Simbec-Orion PV within 24 hours of the time the information is known. Consent to report information regarding pregnancy outcomes should be obtained from the mother. Pregnancy is not regarded as an AE.

If the pregnancy outcome meets the SAE definition also complete an SAE Form. It is important to monitor the outcome of any pregnancies of participants in order to provide SAE data on congenital anomalies, birth defects or spontaneous abortion.

### 10.9.18 Laboratory Safety Assessments

#### Laboratory Safety Screen

Laboratory safety screen samples will be analysed by Simbec-Orion Laboratory Services. Printed laboratory test result reports will include normal reference ranges. A decision regarding whether the laboratory test result outside the normal reference range is of clinical significance or not shall be made by an Investigator/designee and the report will be annotated accordingly. Clinically significant laboratory test result abnormalities will be recorded on the AE page. The normal reference ranges for laboratory test parameters will be detailed in the SLPDoc0024 Normal Reference Ranges and Alert Reference Values document.

**Biochemistry Tests:** Alanine transaminase (ALT), albumin, alkaline phosphatase (ALP), aspartate transaminase (AST), bicarbonate, total bilirubin, direct bilirubin (if total bilirubin is raised), calcium (Ca), chloride (Cl) c-reactive protein (CRP), creatine kinase (CK), creatinine, glucose (fasting or random), gamma glutamyltransferase (GGT), potassium (K), total protein, sodium (Na), urea, total serum testosterone and luteinizing hormone (LH).

Blood samples for biochemistry analyses for each time-point will be collected into an appropriately sized serum collection tube with or without a separator, and analysed by Simbec-Orion Laboratory Services, or at an appropriate referral laboratory, using an appropriate analyser/method(s) of analyses. Assessments of blood sample quality (i.e., for sample verification) will be performed by measuring 3 indices [namely, Lipaemic (for Lipaemia), Haemolytic (for Haemolysis) and Icteric (for Icterus)] in serum.

**Haematology Tests:** Haemoglobin (Hb), haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), platelet count, red blood cell count (RBC), red blood cell distribution width (RDW), white blood cell count (WBC), and WBC differential count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) (reported in absolute and percentage values).
Blood samples for haematology analyses for each time-point will be collected into an appropriately sized blood collection tube containing ethylenediaminetetraacetic acid (EDTA) and analysed by Simbec-Orion Laboratory Services, or at an appropriate referral laboratory, using an appropriate analyser/method(s) of analyses.

**Coagulation Tests:** Activated partial thromboplastin time (aPTT) and prothrombin time (PT)

Blood samples for coagulation analyses for each time-point will be collected into an appropriately sized plasma collection tube containing buffered trisodium citrate solution (0.105 M or 0.109 M, equivalent to 3.2% trisodium citrate) and analysed by Simbec-Orion Laboratory Services, or at an appropriate referral laboratory, using an appropriate analyser/method(s) of analyses.

**Urinalysis Tests:** Bilirubin, blood, glucose, ketones [or ketone bodies], leucocytes, nitrite, pH, protein, specific gravity (SG), and urobilinogen.

A mid-stream urine sample for each time-point will be collected into a 20 mL collection/storage container. Urinalysis will be performed by Simbec-Orion Laboratory Services, or at an appropriate referral laboratory, using an appropriate analyser/manual kit(s)/method(s) of analyses.

In the event that the urinalysis 'dipstick' test result is positive for nitrite and/or 2+ or more reported for protein, blood, and/or leucocytes, then urine microscopy will be performed by reflex. The following test parameters will be reported: bacteria, casts (non-pathogenic), casts (pathogenic), crystals, epithelial cells, red blood cells and white blood cells. The urine microscopy will be performed by Simbec-Orion Laboratory Services, or at an appropriate referral laboratory, using an appropriate analyser/method(s) of analyses.

### 10.9.19 Other Safety Assessments

**Vital signs:** Systolic/diastolic blood pressure, heart rate, oral body temperature and respiration rate.

Measurements will be recorded in the supine position after 10 min supine. Blood pressure, heart rate and temperature will be measured by the DINAMAP* Compact Vital Signs Monitor (Model TS) or equivalent. Normal ranges for vital signs are presented in Appendix 13.

**Physical Examination**

A physical examination will be performed by an Investigator. The examination will include ear/nose/throat, ophthalmological, dermatological, cardiovascular, respiratory, gastrointestinal, central nervous system, lymph nodes and musculoskeletal. An Investigator can examine other body systems if required, at their discretion.

**12-lead ECG:** Heart rate, PR interval, QRS width, RR interval, QT interval and QT interval corrected using Fredericia's formula (QTcF).

12-lead ECG recordings will be made using a Mortara ELI280 or equivalent. Each ECG trace should be labelled with the study number, participant number, age, gender, and ethnicity. An Investigator will provide an interpretation of each tracing. Clinically significant abnormalities will be recorded on the AE page. Normal ranges for 12-lead ECG parameters are presented in Appendix 13.

**Concomitant Medication**

All prior and concomitant medications taken during the study will be recorded in the participant's eCRF (see Section 10.8.12).

### 10.9.20 Appropriateness of Measurements

All measurements performed in the study are standard measurements.

The total volume of blood to be collected from each participant during each part of the study will not exceed 500 mL and is considered acceptable (Table 10.9.4, Table 10.9.5, Table 10.9.6).

## Table 10.9.4 Part A (Single Ascending Dose) Summary of Blood Volume

| Procedure | Visit | Number of Samples | Blood Volume per Sample (mL) | No. Treatment Periods | Blood Volume (mL) |
|---|---|---|---|---|---|
| **Biochemistry**[1] | Screening | 1 | 4.5 | N/A | 4.5 |
| | Treatment Period | 4 | 4.5 | 1 | 18.0 |
| **Haematology** | Screening | 1 | 3.0 | N/A | 3.0 |
| | Treatment Period | 4 | 3.0 | 1 | 12.0 |
| **Coagulation** | Screening | 1 | 2.7 | N/A | 2.7 |
| | Treatment Period | 4 | 2.7 | 1 | 10.8 |
| **PK Drug Conc. Measurement – AX-158** | Treatment Period | 14 | 4.0 | 1 | 56.0 |
| **Exploratory PD samples** | Treatment Period | 2 | 2.7 | 1 | 5.4 |
| | | | | Total Blood Volume[2] | 112.4 |

| Footnotes: | |
|---|---|
| **1** | The biochemistry blood sample collected at the Screening visit will also be used to complete the virology screen (HBsAg, HCV Ab, and HIV). |
| **2** | Please note: This total blood volume does not include any additional blood sample collection(s) for retest, unscheduled testing or additional tests required at the discretion of the Investigator/designee. The exact volumes of each sample may change but the total volume of blood drawn for any participant will not exceed 500 mL. |

## Table 10.9.5 Part B (Food Effect) Summary of Blood Volume

| Procedure | Visit | Number of Samples | Blood Volume per Sample (mL) | No. Treatment Periods | Blood Volume (mL) |
|---|---|---|---|---|---|
| **Biochemistry**[1] | Screening | 1 | 4.5 | N/A | 4.5 |
| | Treatment Period | 3 | 4.5 | 2 (+follow up) | 31.5 |
| **Haematology** | Screening | 1 | 3.0 | N/A | 3.0 |
| | Treatment Period | 3 | 3.0 | 2(+follow up) | 21 |
| **Coagulation** | Screening | 1 | 2.7 | N/A | 2.7 |
| | Treatment Period | 3 | 2.7 | 2(+follow up) | 18.9 |
| **PK Drug Conc. Measurement – AX-158** | Treatment Period | 14 | 4.0 | 2 | 112 |
| | | | | Total Blood Volume[2] | 193.6 |

| Footnotes: | |
|---|---|
| **1** | The biochemistry blood sample collected at the Screening visit will also be used to complete the virology screen (HBsAg, HCV Ab, and HIV). |
| **2** | Please note: This total blood volume does not include any additional blood sample collection(s) for retest, unscheduled testing or additional tests required at the discretion of the Investigator/designee. The exact volumes of each sample may change but the total volume of blood drawn for any participant will not exceed 500 mL. |

**Table 10.9.6 Part C (Multiple Ascending Doses) Summary of Blood Volume**

| Procedure | Visit | Number of Samples | Blood Volume per Sample (mL) | No. Treatment Periods | Blood Volume (mL) |
|---|---|---|---|---|---|
| **Biochemistry**[1] | Screening | 1 | 4.5 | N/A | 4.5 |
| | Treatment Period | 7 | 4.5 | 1 | 31.5 |
| **Haematology** | Screening | 1 | 3.0 | N/A | 3.0 |
| | Treatment Period | 7 | 3.0 | 1 | 21 |
| **Coagulation** | Screening | 1 | 2.7 | N/A | 2.7 |
| | Treatment Period | 7 | 2.7 | 1 | 18.9 |
| **PK Drug Conc. Measurement – AX-158** | Treatment Period | 29 | 4.0 | 1 | 116 |
| **Exploratory PD** | Treatment Period | 2 | 2.7 | 1 | 5.4 |
| | | | | Total Blood Volume[2] | 203 |

| Footnotes: | |
|---|---|
| **1** | The biochemistry blood sample collected at the Screening visit will also be used to complete the virology screen (HBsAg, HCV Ab, and HIV). |
| **2** | Please note: This total blood volume does not include any additional blood sample collection(s) for retest, unscheduled testing or additional tests required at the discretion of the Investigator/designee. The exact volumes of each sample may change but the total volume of blood drawn for any participant will not exceed 500 mL. |

### 10.9.21 Primary Efficacy Variable(s)

Not applicable.

### 10.9.22 Drug Concentration Measurements

Plasma and urine samples for drug concentration measurements will be analysed at Simbec-Orion Laboratory Services using a validated liquid chromatography tandem mass spectrometry (LC MS/MS) method, according to applicable local SOPs.

### 10.9.23 Pharmacokinetic Blood Sampling

Blood sample (4 mL) for the determination of plasma AX-158 levels will be collected per time-point as specified in Table 10.9.1, Table 10.9.2 and Table 10.9.3. (please refer to the Sample Handling Manual [SHM] for processing instructions).

Immediately after sample collection, each sample collection tube will be identified with a barcoded label bearing details of the study number, participant number, sampling time-point, sample type (i.e., sample matrix, e.g., blood, etc.), and a unique 9-digit sample identification number. The date and time at which each PK sample are collected, received in the separating room, and subsequently placed in the appropriate freezer(s) will be recorded in the study documentation.

Full details of sample handling and processing can be found in the SHM.

Should a PK sample not be suitable for sample processing or analysis e.g., severely haemolysed sample, these can be repeated once only.

### 10.9.24 Pharmacokinetic Urine Collection

Urine samples will be collected in Part C for the determination of AX-158 level in urine at the time-points specified in Table 10.9.3.

Each urine collection container will be identified with a barcoded label bearing details of the study number, participant number, sampling time-point, sample type (i.e., sample matrix, e.g., blood, etc), and a unique 9-digit identification number.

The urine collection containers will be kept chilled (at approximately 4°C) during the collection intervals. After the termination of each fractional urine collection interval, the urine volume excreted will be recorded and two 10 mL aliquots retained for the determination of AX-158 level in urine. Each urine aliquot will be labelled similarly to the original collection container and will be stored at -20°C pending analysis.

Full details of sample handling and processing can be found in the SHM.

### 10.9.25 Pharmacodynamic Assessments

Not Applicable.

### 10.9.26 Other Assessments

Exploratory PD samples will be collected as specified in Table 10.9.1 and Table 10.9.3.
Sample handling procedures will be documented in the relevant sample handling manuals.

## 10.10 Data Quality Assurance

At the time the study is initiated, a representative of Artax Biopharma Inc will thoroughly review the final protocol and eCRFs with the Principal Investigator and site staff. During the course of the study the Monitor will visit the Clinical Unit regularly to check the completeness of the participants' records (including the volunteer (participant) master files, laboratory, and 12-lead ECG print-outs), the accuracy of entries into the eCRFs, the adherence to the final protocol and to ICH GCP E6 (R2) guidelines[2], the progress of enrolment and also to ensure the storage, handling, and accountability of the IMP. The Principal Investigator and key study personnel will be available to assist the Monitor during these visits.

The Principal Investigator will give the Monitor, Auditor(s), the REC, and the MHRA direct access to relevant clinical records to confirm their consistency with the CRF entries. No information in these records about the identity of the participants will leave Simbec-Orion.

Artax Biopharma Inc will maintain the confidentiality of all participant records, in line with Section 6.10 of the ICH GCP E6 (R2) guidelines [2].

Study data will be fully documented in the eCRFs and study logbooks. Dated signatures will be given to account for all interventions in the study by research staff.

Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

For the purposes of this study the source data will be recorded as detailed in Table 10.10.1.

## Table 10.10.1 Summary of Source Documentation Location

| Data | eCRF[1]* | Paper Source File | | |
|---|---|---|---|---|
| | | Volunteer Master File | Clinic Source File | Other Study Documentation |
| Evidence of healthy participant status/primary disease condition for entry into clinical study | | X | | |
| Demographic data (e.g., age, year of birth, gender) | | X | | |
| Demographic data (e.g., race, ethnicity, height, weight, and BMI) | X | | | |
| Medical history | | X | | |
| Inclusion and exclusion criteria | | | X | |
| Informed consents[2] | | | | X |
| Participant involvement in the clinical study | X | | | |
| Screening number | | | | X (screening log) |
| Participant number | | | | X (enrolment log) |
| AEs | X | | | |
| SAEs | | | | X (SAE form) |
| Pregnancies | | | | X (Pregnancy notification and outcome form) |
| Previous and on-going therapy | | X | | |
| Concomitant medication | X | | | |
| Results of study examinations (e.g., 12-lead ECGs and laboratory safety tests)[3] | | | X | |
| Vital Signs | X | | | |
| Physical Examination[4] | X | | | |
| Study visit dates | X | | | |
| Administration of IMP | X | | | |
| Blood PK sample collection times | X | | | |
| Urine PK sample collection times | | | | X (log book) |
| Blood safety sample collection times | | | X (test request form) | |
| Urine safety sample collection times | | | X (test request form) | |
| Blood PD sample collection times | X | | | |

1. In the event staff are unable to enter data directly into the eCRF (e.g., technical/internet issues), data will be entered directly into a back-up paper source workbook at the time of assessment, then transcribed and subsequently QC'd.
2. The original informed consent forms will be maintained in the study officer file during the clinical phase and will then be transferred to the Project Manager for archiving with the Investigator Site File at the end of the study.
3. The 12-lead ECG trace and laboratory safety test print-out including medical review will be stored in the paper source file.
4. In the eCRF, the date and time of each physical examination will be recorded. Any abnormal findings will be captured on the Medical History form at Screening and as an Adverse Event during clinical conduct.

AE = adverse event, CRF = case report form/eCRF = electronic case report form, ECG = electrocardiogram, IMP = investigational medicinal product, PK = pharmacokinetic, SAE = serious adverse event.

The above table indicates where source data will be recorded but for completeness the following information will also be recorded in the volunteer master file:

- Clinical study code.
- Study visit dates (pre-dose; post-dose).
- IMP administration (date of last dose).
- Results of any key safety and efficacy measures from the clinical study that, in the opinion of an Investigator, should be noted.
- Any concomitant medications used to treat the participant during the study that, in the opinion of an Investigator, should be noted.

The data collected in the eCRFs during the study will be subject to quality control checking by clinical staff prior to sign off.

Designated investigator site staff will enter the data required by the protocol into the eCRFs using fully validated software that conforms to 21 CFR Part 11 requirements. Staff will not be given access to the eCRF until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the Biometrics group. The Investigator must certify that the data entered into the eCRF are complete and accurate.

The study will be subject to an independent audit by the Simbec-Orion Quality Assurance Unit as outlined in Simbec-Orion SOP GRP-QA 002.

Independent clinical quality assurance audits may be performed at any time during or following completion of the study by the Sponsor, or its authorised agents, and Regulatory Authorities and/or the REC.

## 10.11 Statistical Methods and Determination of Sample Size

### 10.11.1 Statistical and Analytical Plan

A statistical analysis plan (SAP) will be written by Simbec-Orion and agreed by Artax Biopharma Inc prior to the locking of the database and subsequent reporting of the study data.

### 10.11.2 Study Variables/Endpoints

**Part A (SAD):**

The following plasma PK endpoints will be derived: $C_{max}$, $T_{max}$, $\lambda z$, $t_{1/2}$, $AUC_{0-24}$, $AUC_{0-t}$, $AUC_{0-inf}$, $AUC_{\%extrapolated}$, CL/F, Vz/F.

**Part B (Food Effect):**

The following plasma PK endpoints will be derived: $C_{max}$, $T_{max}$, $T_{lag}$, $\lambda z$, $t_{1/2}$, $AUC_{0-24}$,$AUC_{0-t}$, $AUC_{0-inf}$, $AUC_{\%extrapolated}$, CL/F, Vz/F.

**Part C (MAD):**

The following plasma PK endpoints will be derived on Day 1: $C_{max}$, $T_{max}$ and $AUC_{0-24}$, ($AUC_{0-\tau}$ will also be derived if dosing interval other than q.d).

The following plasma PK endpoints will be derived on Final Dosing Day : $C_{max}$, $T_{max}$, $\lambda z$, $t_{1/2}$, $AUC_{0-24}$, ($AUC_{0-\tau}$ will also be derived if dosing interval other than q.d)., $AUC_{0-t}$, $AUC_{0-inf}$, $AUC_{\%extrapolated}$, CL/F and Vz/F.

The following urine PK parameters will be derived on Day 1 and Final Dosing Day: Ae, Ae%, $CL_R$.

**Safety endpoints:**

- AEs.
- Laboratory safety (biochemistry, haematology, coagulation, and urinalysis).
- Vital signs (systolic/diastolic blood pressure, heart rate, oral body temperature and respiratory rate).
- 12-lead ECG (Heart rate, PR interval, QRS width, RR interval, QT interval and QT interval corrected using Fredericia's formula (QTcF).

### 10.11.3Analysis Sets

**Safety Set:** All randomised participants who receive at least 1 dose of IMP will be included in the safety analysis.

**PK Set:** The PK set will include participants who receive IMP (one dose in Part A, both doses in Part B (fed/fasted), up to 10 doses in Part C), have sufficient plasma concentration-time profiles and comply with the following criteria:

- Do not have an occurrence of vomiting (that occurs at or before 2 times median $T_{max}$ within the appropriate cohort or treatment) or diarrhoea which renders the concentration profile unreliable; For Part C this applies to PK sampling days only
- Do not use a concomitant medication which renders the concentration profile unreliable;
- Do not have a Day 1 pre-dose concentration that is greater than 5% of the corresponding $C_{max}$;
- Have at least one pharmacokinetic sample with concentration above the lower limit of quantitation (LLOQ);
- Do not violate the protocol in such a way that may invalidate or bias the results (major protocol violators).

### 10.11.4 Description of Statistical Methods

All statistical analysis will be performed using SAS® (the most up to date version will be used and this will be documented in the SAP).

### 10.11.5 Demographic and Background Data

All demographic and background data will be listed, in addition:

**Disposition:** Participant disposition will be listed with any withdrawals flagged. Frequencies (number and %) of the total number of participants dosed, completed, and prematurely

discontinued (including reason for discontinuation) from the study will be summarised. Additionally, the frequency of participants within each analysis set will be summarised.

**Demographics:** Demographic data will be listed. Descriptive statistics (number of participants in the analysis set (N), number of participants with non-missing observations (n), mean, standard deviation (SD), minimum, median, and maximum) will be tabulated for the continuous variables age, height, weight and BMI and frequencies (number and %) for the categorical variable race.

### 10.11.6 Efficacy Data

Not applicable.

### 10.11.7 Safety Data

All safety data will be listed, in addition:

**AEs:** All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (the most up to date version that is available at the time of database build will be used and will be listed in the Data Management Plan (DMP)). The MedDRA dictionary will not be updated during the course of the study.

All AEs, including those which occurred prior to the first dose of IMP, will be listed. Only treatment emergent adverse events (TEAEs), i.e., existing conditions that worsen or events that occur during the course of the study after administration of IMP, will be included within the summary tables.

An overall summary of AEs will be produced including the number of TEAEs; the number and % of participants reporting at least 1 TEAE, serious TEAE, TEAE leading to withdrawal from the study; the number and % of participants reporting TEAEs by severity and relationship to IMP.

The number of TEAEs and the number and % of participants reporting at least 1 TEAE will be tabulated by system organ class (SOC) and preferred term. A participant reporting multiple episodes of a particular AE within a treatment period will only contribute 1 count towards the corresponding SOC and preferred term.

The number of TEAEs and the number and % of participants reporting at least 1 TEAE will be tabulated by preferred term and sorted by descending frequency on the total number of participants with that AE. A participant reporting multiple episodes of a particular AE within a treatment period will only contribute 1 count towards the corresponding preferred term.

In addition, the number and % of participants reporting TEAEs will be tabulated by maximum severity and strongest relationship to IMP. For the summary of TEAEs by severity, if a participant has multiple events occurring within the same SOC or preferred term the event with the highest severity will be counted. Similarly, for TEAEs by relationship to IMP, if a participant has multiple events occurring within the same SOC or preferred term, the event with the highest association to IMP will be counted.

**Laboratory Safety:** Biochemistry, haematology, coagulation, and urinalysis parameters will be listed with any out of normal range values flagged. Laboratory test results which are out of normal range will also be presented separately along with normal reference ranges. Descriptive

statistics (N, n, mean, SD, minimum, median, and maximum) of absolute and change from baseline (Day 1, pre-dose) values at each protocol-defined time point will be tabulated.

**Vital Signs:** Vital signs parameters will be listed with any out of normal range values flagged. Descriptive statistics (N, n, mean, SD, minimum, median, and maximum) of absolute and change from baseline (Day 1, pre-dose) values at each time point will be tabulated.

**12-Lead ECG:** 12-Lead ECG parameters will be listed with any out of normal range values flagged. Descriptive statistics (N, n, mean, SD, minimum, median, and maximum) of absolute and change from baseline (Day 1, pre-dose) values at each time point will be tabulated.

Additionally, the frequency (number and % of participants) for absolute and change from baseline QTcF values will be summarised according to the below categories:

For absolute values

- QTcF $\leq$ 450 msec
- 450 < QTcF $\leq$ 480 msec
- 480 < QTcF $\leq$ 500 msec
- QTcF > 500 msec.

For change from baseline

- Decrease/no change
- QTcF increase $\leq$ 30 msec
- 30 < QTcF increase $\leq$ 60 msec
- QTcF increase > 60 msec.

### 10.11.8 PK Data

***Concentration-Time Data:*** Individual plasma and urine AX-158 concentration-time data will be listed. Plasma and urine concentration-time data will also be summarised. The descriptive statistics presented will be N, n, arithmetic mean, geometric mean, SD, coefficient of variation (CV%), minimum, median, and maximum. Individual and mean plasma concentration-time data will also be plotted on both linear and semi-logarithmic scales.

For the purposes of summarising and plotting concentration-time data, concentration value(s) below the LLOQ will be assigned a value of zero if the timepoint is prior to treatment and LLOQ/2 otherwise.

***Derived PK Data:*** The following PK parameters will be derived from plasma and urine AX-158 concentration-time data following administration of IMP using Phoenix WinNonlin (the most up to date version will be used and this will be documented in the SAP). Additional parameters may be reported as appropriate.

For the purposes of calculating PK parameters, concentration value(s) below the LLOQ will be assigned a value of missing.

***Plasma:***

- $C_{max}$ Maximum concentration.
- $T_{max}$ The time to maximum observed concentration.
- $T_{lag}$ The delay in achieving $T_{max}$
- $\lambda z$ Elimination rate constant.
- $t_{1/2}$ Terminal elimination half-life.
- $AUC_{0-24}$ Area under the concentration-time curve (AUC) from 0 to 24 h post-dose.
- $AUC_{0-\tau}$ Area under the concentration-time curve (AUC) from 0 to $\tau$, where $\tau$ is the dosing interval (planned, 0 - 24 h) (Part C only).
- $AUC_{0-t}$ Area under the concentration-time curve (AUC) from the time of dosing to the time of the last measurable concentration.
- $AUC_{0-inf}$ AUC extrapolated to infinity.
- $AUC_{\% extrapolated}$ Residual area.
- CL/F Total apparent clearance following extravascular administration.
- Vz/F Apparent volume of distribution following extravascular administration.

***Urine***

- Ae Amount and cumulative amount of dose excreted in urine over each collection interval.
- Ae% % and cumulative % of dose excreted in urine over each collection interval.
- $CL_R$ Renal clearance.

Derived PK parameters will be listed along with the points used to calculate $k_{el}$ (lower, upper, and number used) and coefficient of determination ($R^2$) adjusted. The derived PK parameters will also be summarised. The descriptive statistics presented will be N, n, arithmetic mean, geometric mean (with the exception of $T_{max}$), SD, coefficient of variation (CV%), minimum, median, and maximum.

**Part A (SAD):** *Dose Proportionality/Independence.* Dose proportionality will be assessed by performing a regression analysis of the log-transformed $C_{max}$, $AUC_{0-t}$ and $AUC_{0-inf}$ values versus the log-transformed dose using the power model with a fixed effect for log (dose). For each parameter, a point estimate and 95 % confidence interval (CI) will be calculated for the slope of the regression line.

Dose independence will be assessed for t½ and CL/F by performing a regression analysis of the untransformed parameters versus dose with a fixed effect for dose. For each parameter, a

point estimate and corresponding 95 % CI will be calculated for the slope of the regression line.

**Part B (Food Effect):** Following logarithmic transformation, $C_{max}$, $AUC_{0-t}$ and $AUC_{0-inf}$ values will be subjected to an ANOVA including fixed effects for treatment and participant. Point estimates and 90% CI will be constructed for the contrasts between treatments using the residual mean square error obtained from the ANOVA. The point and interval estimates will be back-transformed to give estimates of the ratios of the geometric least squares means (LSmeans) and corresponding 90% CI. Estimated geometric means will also be presented for each treatment.

**Part C (MAD)**

*Dose Proportionality/Independence:* For Day 1 and Final Dosing Day (Day 10), dose proportionality will be assessed by performing a regression analysis of the log-transformed $C_{max}$, $AUC_{0-\tau}$ and $AUC_{0-inf}$ (Day 1 only) values versus the log-transformed dose using the power model with a fixed effect for log (dose). For each parameter, a point estimate and 95 % CI will be calculated for the slope of the regression line.

For Final Dosing Day (Day 10), dose independence will be assessed for t½ and CL/F by performing a regression analysis of the untransformed parameters versus dose with a fixed effect for dose. For each parameter, a point estimate and corresponding 95 % CI will be calculated for the slope of the regression line.

*Steady-State:* For each dose level, log-transformed trough concentration levels at pre-dose day 5 will be subjected to a mixed effects ANOVA with study day as a fixed effect and participant as a random effect in order to establish whether and when steady-state has been attained for each dose level. Back-transformed ratios for the comparisons of each consecutive day (i.e., Day 3/Day 2) will be presented along with corresponding 90 % CI.

*Accumulation:* For each dose level, log-transformed $C_{max}$ and $AUC_{0-\tau}$ values on Day 1 and Final Dosing Day (Day 10) will be subjected to an ANOVA with study day as a fixed effect and participant as a random effect. For comparison, point estimates and 90 % CI for the difference between Final Dosing (Day10) and Day 1 will be constructed using the residual mean square error obtained from the ANOVA for each dose level. The point and interval estimates will then be back transformed to give estimates of the ratios of the geometric least squares means and corresponding 90 % CI.

### 10.11.9 Other Data

Not applicable.

### 10.11.10 Sample Size Calculation

The sample size chosen for this study is not based on a formal statistical estimation but is considered adequate to meet the objectives of the study. A sufficient number of participants will be initially screened for enrolment to ensure that the planned sample size is achieved.

# 11 PRACTICAL CONSIDERATIONS

## 11.1 Storage of Data

The Investigator site file and associated study documentation will be archived for at least 25 years after the end of the study (last participant last visit) as per European Medicine Agency Guideline (EMA) INS/GCP/856758/2018 [4]. The study documentation may be transferred to an offsite storage facility during this period but will remain under the control of Simbec-Orion.

The Sponsor has delegated the set up and maintenance of the Sponsor trial master file (TMF) to Simbec-Orion. The TMF will be returned to the Sponsor at the end of the study, who will archive it for at least 25 years after the end of the study.

## 11.2 Protocol Amendments

Changes in the study protocol must take the form of written protocol amendments and shall require the approval of all persons responsible for the study (see Section 1).

A protocol amendment is deemed to constitute a substantial protocol amendment if it is considered to affect a significant degree either:

a. The safety or physical or mental integrity of the participants of the study.

b. The scientific value of the study.

c. The conduct or management of the study.

d. The quality or safety of any IMP used in the study.

Such amendments must be submitted to the REC responsible for the study and the MHRA for approval prior to implementation.

Protocol amendments required for urgent safety reasons may be implemented immediately. However, the REC and MHRA must be notified in writing within 3 days of the measures taken and the reasons for implementation.

All other amendments shall be deemed to be non-substantial and as such do not need the prior approval of the REC and the MHRA.

## 11.3 Confidentiality

The confidentiality of the study must be maintained at all times, and the Principal Investigator must not reveal any information relating to the study without express permission from the study Sponsor.

## 11.4 Study Report and Publication Policy

The Principal Investigator will obtain the Sponsor's written permission before any information concerning this study is submitted for publication.

## 11.5 General Data Protection Regulation (GDPR)

Personal data of the participant shall be processed in a manner that ensures it has appropriate security. This includes protection against unauthorised or unlawful processing and against

accidental loss, destruction, or damage and by using appropriate technical or organisational measures. One such measure is by the Investigator ensuring that the participants' personally identifiable information should be replaced through the use of pseudonymisation.

On the eCRFs or other documents submitted to Artax Biopharma Inc/Simbec-Orion participants will NOT be identified by their names but by the assigned participant number (panel/screening/participant number) to ensure confidentiality of the participants' information and that data minimisation principles are maintained. If participant names are included in error on copies of documents submitted to Artax Biopharma Inc Simbec-Orion participants', the names (except for initials) will be erased or securely destroyed and the assigned participant number added to the document.

# 12 REFERENCES

[1] Current version of AX-158 Investigator's Brochure (IB).

[2] ICH (International Council on Harmonisation). Guideline for Good Clinical Practice (GCP) E6 (R2) (CPMP/ICH/135/95) 2016.

[3] Current version of AX-158 Investigational Medicinal Product Dossier (IMPD).

[4] EMA (European Medicine Agency). Guideline on the Content, Management and Archiving of the Clinical Trial Master File (paper and/or electronic) INS/GCP/856758/2018.

[5] FDA. 2002. Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/food-effect-bioavailability-and-fed-bioequivalence-studies

[6] Ec.europa.eu. 2015. EudraLex - Volume 4 Good Manufacturing Practice (GMP) Guidelines. - European Commission. [online] Available at: https://ec.europa.eu/health/documents/eudralex/vol-4_en

# 13 APPENDIX 1: NORMAL RANGES FOR VITAL SIGNS AND ECG PARAMETERS

| Vital Sign Parameters | | |
|---|---|---|
| **Parameter** | **Normal Range** | **Units** |
| Heart Rate | 40-100 | beat(s) per minute (bpm) |
| Systolic Blood pressure | 90-140 | millimetre(s) of mercury (mmHg) |
| Diastolic Blood pressure | 50-90 | millimetre(s) of mercury (mmHg) |
| Respiratory Rate | 12-18 | breath(s) per minute |
| Oral Temperature | 35.0-37.5 | degrees Celsius (ºC) |

| ECG Parameters | | |
|---|---|---|
| **Parameter** | **Normal Range** | **Units** |
| Heart Rate | 40-100 | beat(s) per minute (bpm) |
| PR Interval | 120-220 | millisecond(s) (ms) |
| QRS Width | 70-120 | millisecond(s) (ms) |
| QT Interval | N/A | N/A |
| QTc Interval (Fridericia's Formula) | Male: 350-450 | millisecond(s) (ms) |

# 14 APPENDIX 2: DECLARATION OF HELSINKI (BRAZIL, 2013)

https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

# AMENDMENT ASSESSMENT FORM

This form serves to document the decision on whether the amendment is considered substantial or non-substantial. It is the responsibility of the sponsor to determine whether an amendment is substantial.

If the sponsor is satisfied that an amendment is not substantial, there is no requirement to notify the Competent Authority or Ethics Committee. Although non-substantial amendments may be notified to the Competent Authority or Ethics Committee for information only based on local requirements.

## Substantial Amendment

In accordance with EC guidance 2010/C 82/01 (CT-1), amendments to the trial are regarded as 'substantial' where they are likely to have a significant impact on:

- The safety or physical or mental integrity of the clinical trial participants or
- The scientific value of the trial

## Non-substantial Amendment

A Non-substantial amendment does not meet the criteria listed above.

## Further Guidance

Please see the following for more guidance:

- EC guidance 2010/C 82/01 (CT-1)
- Local regulations for EU and non-EU member states (for example US 21 CFR for US FDA)
- CHMP/QWP/185401/2004 for IMPs

| | |
|---|---|
| **Sponsor name** | **Artax Biopharma Inc.** |
| EudraCT Number (if applicable): | 2021-002541-16 |
| Simbec-Orion Clinical Pharmacology RD number (Phase I HV studies) / Simbec-Orion Clinical Development internal number | RD 675.34625 |
| Protocol Number: | AX-158-101 |
| Amendment Code: (This is not the same as the protocol amendment code) | SA01 |

List of the regulatory documents impacted by this amendment:

| Document Title | Version & Date | Previous Version & Date |
|---|---|---|
| **Study Protocol** | V4.0 Dated 14 January 2022 | V3.0 Dated 22 October 2021 |
| **Participant Information Sheet & Consent Form – Part A MASTER** | V3.0 Dated 14 January 2022 | V2.0 Dated 22 October 2021 |
| **Participant Information Sheet & Consent Form – Part B MASTER** | V3.0 Dated 14 January 2022 | V2.0 Dated 22 October 2021 |
| **Participant Information Sheet & Consent Form – Part C MASTER** | V3.0 Dated 14 January 2022 | V2.0 Dated 22 October 2021 |

Details of the amendment are described below:

The Sponsor wishes to proceed with this amendment in order to implement changes to the study protocol, and participant information sheet and consent form (PIS) for each respective study part (Part A, Part B & Part C). This amendment affects the study protocol and PIS only; no other subject facing or regulatory documentation is impacted as a result of these changes.

The purpose of the protocol amendment is to introduce a number of changes within the protocol in relation to COVID-19 risk mitigation strategies in response to the evolution of the COVID-19 pandemic in the UK and to introduce blood sampling for the measurement of exploratory pharmacodynamics (PD) within Part A of the study.

With respect to the changes implemented in response to the COVID-19 pandemic, the Sponsor wishes to implement the following revisions. In recognition of the MHRA requirement to conduct ongoing COVID-19 risk/benefit assessments to support the continued conduct of clinical trials in the context of the COVID-19 pandemic, the Sponsor has determined at this stage that it is appropriate to implement new measures in line with the current status of the pandemic within the UK. The risk assessment within

the current approved version of the study protocol (v3.0, Dated 22 October 2021) outlines that participants may be enrolled into the study provided that they have not received a COVID-19 vaccine within the 28 days prior to the first dose of the IMP until the completion of the post-study follow up procedures. The current protocol does not require participants to be vaccinated against COVID-19. The rationale for this assessment is based on the potential for interaction between the IMP and the vaccine, the immunomodulatory nature of the drug and the basis that this is a first-in-human (FiH) study and therefore, the action of the drug is not known in humans as of yet.

However, given the current status of the pandemic within the UK with the evolution of new variants etc., the Sponsor has determined that the protocol, specifically the inclusion criteria for the study should be updated in order to mandate that any participants who are enrolled within the study must have received their full doses of the COVID-19 vaccine as per the current Welsh/UK Government guidelines and that these doses should have been received outside of the defined restriction window defined above. As the definition of 'full' doses is likely to evolve with the continued rollout of the vaccination programme and requirement for follow up booster doses, the language in the protocol will be presented flexibly such that the 'full' dose definition for determining participant eligibility will be reflective of the latest definition at the time of enrolment.

In addition, the Sponsor wishes to update the protocol to include flexibility for the nature and type of COVID-19 testing which may be conducted during the study. As part of the study protocol and in alignment with the COVID-19 risk mitigation strategies implemented at Simbec-Orion in order to support the continued conduct of clinical trials in the context of the ongoing pandemic, COVID-19 PCR antigen testing is a mandatory requirement for all participants undertaking a clinical trial involving overnight stays at the clinical unit. In the context of this study, COVID-19 PCR antigen testing is conducted on Day -1 of each treatment period across all parts of the study.

To date, Simbec-Orion have utilised the Menarini Diagnostics VitaPCR Point of Care analyser to perform Real-Time Polymerase Chain Reaction testing (RT-PCR) using a SARS-CoV-2 assay. This test equipment is CE IVD marked and provides 95% sensitivity and 100% specificity.

However, as of October 2021, it has been highlighted by the manufacturer that as part of a revised UK government approach (COVID Testing Devices Authorisation CDTA), it is a requirement that clinical data should be submitted for review to enable the manufacturer to be included on the list of government approved COVID-19 testing suppliers. At this stage, the manufacturer (Menarini) have advised that until approved they are unable to distribute any further COVID-19 testing kits and as such, in order to mitigate against any potential testing kit shortage, Simbec-Orion proposes to implement an alternative method of COVID-19 testing in the interim period whilst the Menarini kits are pending approval and to provide ongoing flexibility for testing methods as the pandemic evolves further.

Therefore, it is proposed that the protocol will be updated in order to include flexibility for the conduct of Lateral Flow Testing (LFT) as standard routine testing in the first instance, in addition to PCR Antigen Testing as required in order to ensure that there is continuity of testing throughout the study and sufficient measures in place in order to mitigate against the spread of the COVID-19 virus. A risk assessment has been conducted for this approach and confirmed as appropriate as this aligns with the current strategy being implemented across a number of Phase 1 Clinical Trials Units across the UK. It is intended that LFT testing will be the routine method of testing utilised during the ongoing conduct of the study based on kit availability and if necessary, PCR Antigen Testing may be performed as a confirmatory evaluation of a positive LFT test if needed and at the Principal Investigator's discretion. In the circumstances where PCR antigen kit availability stabilises, the testing regime outlined within the study protocol will revert back to PCR testing instead of LFT.

Further to this, the Sponsor wishes to implement a COVID-19 test on Day 8 and prior to discharge on the last day of the treatment period (currently defined as Day 13) of the study for participants who are enrolled to Part C of the study which is the Multiple Ascending Dose (MAD) part of the study. Given the length of the in-house treatment period for Part C whereby participants are resident within the

clinical unit for a minimum period of 14 days (from Day -1 to Day 13), the Sponsor has determined that in order to best mitigate against the potential for development of a COVID-19 positive scenario whilst participants are in-house during this treatment period, the inclusion of additional COVID-19 testing at the half-way point and last day of the treatment period prior to discharge from the clinical unit is appropriate. As the study protocol includes flexibility such that the length of the in-house treatment period may be extended to permit dosing up to 14 days, if this change is implemented based on dose escalation data review, then the timepoints of the COVID-19 testing will be adjusted accordingly such that the testing falls at the half-way point of the treatment period and on the last day of the treatment period prior to discharge from the clinical unit (defined as 72 hours post-last dose of AX-158).

With respect to the other aspects of this protocol amendment, the Sponsor wishes to introduce blood sampling for the measurement of exploratory pharmacodynamics (PD) within Part A of the study. Within the current approved version of the study protocol (v3.0, Dated 22 October 2021), an adaptive design element has been included such that exploratory PD samples may be taken at selected timepoints within Part C (MAD) of the study based on emerging data from Part A (SAD) and Part B (Food Effect). At present, these timepoints are not defined due to the fact that Part A of the study is ongoing. Therefore, timepoints for exploratory PD sampling within Part C of the study will be defined following dose escalation data review of Part A and Part B data as indicated. However, following evaluation of the study protocol, the Sponsor now wishes to include the performance of exploratory PD sampling within Part A of the study (to be implemented from Cohort 3 onwards and for all subsequent Part A cohorts). Therefore, the protocol will be updated in order to include reference to this sampling. The intention is that two exploratory PD samples will be taken: one at pre-dose on Day 1 in Part A and Part C (serving as the baseline control) and a second sample at a defined timepoint. At present, the timing of the second exploratory PD sample within Part A and Part C is to be defined and will be confirmed following dose escalation data review of Cohort 2 PK data from Part A for the timepoint in Part A of the study and following dose escalation data review of Part A and Part B data for the timepoint with respect to the Part C of the study. These measures are exploratory in nature and do not contribute to the overall evaluation of the study objectives and will apply to all cohorts within Part A from Cohort 3 onwards and all Part C cohorts.

Therefore, this amendment serves to implement the changes as described above.

**Substantial Amendment – Study Protocol v4.0 (14 January 2022)**

As described above, the scope of the substantial amendment impacts the study protocol.

The scope of the protocol changes in protocol v4.0 (14 January 2022) are as follows:

| Protocol Section | Section Change |
|---|---|
| Protocol Section 3 - Synopsis | - Updated to align with changes in main body text |
| Protocol Section 5 - Abbreviations | – Minor updates to abbreviations list to include Lateral Flow Test (LFT) |
| Protocol Section 8.8 - Coronavirus Disease 2019 (COVID-19) Risk/Benefit Assessment | - Risk/benefit assessment updated to reflect the requirement for all participants enrolled into the study to be fully vaccinated against COVID-19 as per the current Welsh/UK Government guidelines |
| Protocol Section 10.2 – Adaptive Elements | - Adaptive design elements updated to indicate that the timing of exploratory PD samples in both |

| | |
|---|---|
| | Part A and Part C of the study will be taken at pre-dose on Day 1 in both parts and at an additional timepoint to be determined based on emerging data generated during the study. |
| Protocol Section 10.5.1 – Inclusion Criteria | - Criterion #16 updated to remove reference to the specific type of COVID-19 testing with text updated to reflect the requirement for a negative COVID-19 test at admission<br><br>- New criterion #17 added to reflect the requirement for all participants enrolled into the study to be fully vaccinated against COVID-19 as per the current Welsh/UK Government guidelines |
| Table 10.9.1 – Study Flow Chart Part A Single Ascending Dose | - Flow chart updated to remove reference to the specific type of COVID-19 testing on Day -1 of the treatment period<br><br>- Flow chart updated to include timepoints for exploratory PD sampling |
| Table 10.9.2 – Study Flow Chart Part B Food Effect | - Flow chart updated to remove reference to the specific type of COVID-19 testing on Day -1 of each treatment period |
| Table 10.9.3 – Study Flow Chart Part C Multiple Ascending Dose | - Flow chart updated to remove reference to the specific type of COVID-19 testing on Day -1, Day 8 and the last day of the treatment period (i.e., discharge from the clinical unit 72 hours post-last dose of AX-158)<br><br>- Flow chart updated to include COVID-19 testing on Day 8 and on the last day of the in-house treatment period (i.e., discharge from the clinical unit 72 hours post-last dose of AX-158)<br><br>- Flow chart updated to include timepoints for exploratory PD sampling |
| Protocol Section 10.9.6 – COVID-19 Testing | - Section updated to reference routine performance of Lateral Flow Testing in each respective study part with the option to perform COVID-19 PCR Antigen testing at the Principal Investigators' discretion |
| Table 10.9.4 - Part A (Single Ascending Dose) Summary of Blood Volume | - Blood volume updated to reflect addition of exploratory PD samples |

| | |
|---|---|
| Table 10.9.6 - Part C (Multiple Ascending Dose) Summary of Blood Volume | - Blood volume updated to reflect addition of exploratory PD samples |
| Protocol Section 10.9.26 – Other Assessments | - New section added to describe the procedures for collection of exploratory PD samples |
| Protocol Section 10.10.1 – Summary of Source Documentation Location | - Addition of reference to PD sample collection |
| Protocol Section 10.11.2 – Study Variables/Endpoints | - Endpoints for derived plasma PK for all study parts updated to include $AUC_{0-24}$ |
| Protocol Section 10.11.8 – PK Data | - Text updated to include $AUC_{0-24}$ |

As a result of the protocol changes described above, the participant information sheet and consent form for each respective study part will be updated. No other subject facing or regulatory documentation is impacted as a result of these changes.

On the basis of the changes and in consideration of the relevant guidance, the Sponsor has determined that the changes detailed above are considered substantial in nature and therefore the updated study protocol and associated participant facing documents will require review and approval by the ethics committee and MHRA.

In addition, as per standard practice, this amendment will notify all previous non-substantial amendments which have been implemented since the point of the last approval issued by the ethics committee and MHRA.

In the context of this study, this will incorporate the notification of the following amendment:

- **Non-Substantial Amendment 01 (NSA01)** – Affecting the protocol, IMPD and other associated participant facing documents. Details of this amendment may be found in NSA01 amendment assessment form v1.0 (22 October 2021).

The sponsor considers this amendment to be:

Note: The categories listed below are extracted from the Annex 2 form (Notification of Substantial Amendment Form).

| | | Please confirm appropriate option |
|---|---|---|
| **Substantial** | ☒ | Category#: D |
| **Non-Substantial** | ☐ | |

| | |
|---|---|
| **A** | **Changes in safety or integrity of trial subjects** |
| **B** | **Changes in interpretation of scientific documents/value of the trial** |

| | |
|---|---|
| **C** | **Changes in quality of IMP(s)** |
| **D** | **Changes in conduct or management of the trial** |
| **E** | **Change or addition of principal investigator(s), coordinating investigator** |
| **F** | **Change/addition of site(s)** |
| **G** | **Other change - Please specify:** |

Type of Notification (Approval or Notification Only)

| | |
|---|---|
| Competent Authority approval required: | ☒ |
| Ethics Committee(s) approval required: | ☒ |
| Other approval (e.g. HRA, ARSAC etc) required: Please specify: | ☐ |
| Competent Authority approval not required (No notification): | ☐ |
| Ethics Committee approval not required (No notification): | ☐ |

**COMPLETED BY REGULATORY LEAD:**

Gabrielle Brill

Senior Regulatory Affairs Associate

Signature:

Date:

DocuSigned by:
Gabrielle Brill
Signer Name: Gabrielle Brill
Signing Reason: I am the author of this document
Signing Time: 14-Jan-2022 | 21:01 GMT
71021EA46C4D41878477EAB25CD472C4

**PROJECT MANAGER:**

Adam Chessun

Senior Project Manager

Signature:

Date:

DocuSigned by:
Adam Chessun
Signer Name: Adam Chessun
Signing Reason: I approve this document
Signing Time: 17-Jan-2022 | 09:05 GMT
79E7AB1F2BCB4A0D8AC7262A8FD2CDDB

**STUDY SPONSOR:**

Andres Gagete

Chief Operating Officer

Signature:

Date:

DocuSigned by:
Andres Gagete
Nombre del firmante: Andres Gagete
Motivo de la firma: He revisado este documento
Hora de firma: 17-ene.-2022 | 00:15 PST
ED1F11BF89194408AA1B9CA5262ADA82

DocuSign

## Certificado de finalización

Identificador del sobre: B8130938F88648A9A0D702D44B11CA17
Estado: Completado
Asunto: Please DocuSign: RD675.34625 (AX-158-101) Clinical Study Protocol v4.0 14 Jan 2022 CLEAN.pdf, R...
Sobre de origen:
Páginas del documento: 93
Firmas: 5
Autor del sobre:
Páginas del certificado: 6
Iniciales: 0
Gabrielle Brill
Firma guiada: Activado
Unit 29 Simbec Research Ltd
Sello del identificador del sobre: Desactivado
Merthyr Tydfil Industrial Park, Pentrebach
Zona horaria: (UTC) Dublín, Edimburgo, Lisboa, Londres
Merthyr Tydfil , Merthyr Tydfil CF464DR
gabrielle.brill@simbecorion.com
Dirección IP: 81.154.157.127

## Seguimiento de registro

Estado: Original
Titular: Gabrielle Brill
Ubicación: DocuSign
14-ene.-2022 | 20:56
gabrielle.brill@simbecorion.com

| Eventos de firmante | Firma | Fecha y hora |
|---|---|---|
| Adam Chessun<br>adam.chessun@simbecorion.com<br>Project Manager<br>Simbec Orion<br>Nivel de seguridad: Correo electrónico, Autenticación de cuenta (obligatoria) | Adam Chessun<br>Adopción de firma: Estilo preseleccionado<br>Identificador de firma: 79E7AB1F-2BCB-4A0D-8AC7-262A8FD2CDDB<br>Utilizando dirección IP: 94.3.16.134<br>Con autenticación de firma a través de la contraseña de DocuSign<br>Con motivos de la firma (en cada pestaña):<br>I approve this document | Enviado: 14-ene.-2022 \| 21:00<br>Visto: 17-ene.-2022 \| 09:05<br>Firmado: 17-ene.-2022 \| 09:05 |
| **Información sobre confidencialidad de registros y firmas electrónicos:**<br>No ofrecido a través de DocuSign | | |
| Andres Gagete<br>agagete@artaxbiopharma.com<br>Nivel de seguridad: Correo electrónico, Autenticación de cuenta (obligatoria) | Andres Gagete<br>Adopción de firma: Estilo preseleccionado<br>Identificador de firma: ED1F11BF-8919-4408-AA1B-9CA5262ADA82<br>Utilizando dirección IP: 81.43.179.190<br>Con autenticación de firma a través de la contraseña de DocuSign<br>Con motivos de la firma (en cada pestaña):<br>He revisado este documento | Enviado: 14-ene.-2022 \| 21:00<br>Visto: 17-ene.-2022 \| 08:10<br>Firmado: 17-ene.-2022 \| 08:15 |
| **Información sobre confidencialidad de registros y firmas electrónicos:**<br>Aceptado: 20-may.-2021 \| 18:22<br>ID: e39e11f4-8ca3-49e0-a566-b657402801d4 | | |

| Eventos de firmante | Firma | Fecha y hora |
|---|---|---|
| Annelize Koch<br>annelize.koch@simbecorion.com<br>Medical Director - Clinical Pharmacology<br>Orion Clinical Services Limited (acting for itself and on behalf of its Affiliates) - Part 11<br>Nivel de seguridad: Correo electrónico, Autenticación de cuenta (obligatoria) |  <br>Adopción de firma: Estilo preseleccionado<br>Identificador de firma: 9B632C24-B4B3-4F7E-8F51-4510788D4968<br>Utilizando dirección IP: 81.150.92.225<br>Firmado con un dispositivo móvil<br>Con autenticación de firma a través de la contraseña de DocuSign<br>Con motivos de la firma (en cada pestaña):<br>I approve this document | Enviado: 14-ene.-2022 \| 21:00<br>Visto: 14-ene.-2022 \| 21:22<br>Firmado: 15-ene.-2022 \| 08:10 |
| **Información sobre confidencialidad de registros y firmas electrónicos:**<br>No ofrecido a través de DocuSign | | |
| Gabrielle Brill<br>gabrielle.brill@simbecorion.com<br>Simbec Orion<br>Nivel de seguridad: Correo electrónico, Autenticación de cuenta (obligatoria) |  <br>Adopción de firma: Estilo preseleccionado<br>Identificador de firma: 71021EA4-6C4D-4187-8477-EAB25CD472C4<br>Utilizando dirección IP: 81.154.157.127<br>Con autenticación de firma a través de la contraseña de DocuSign<br>Con motivos de la firma (en cada pestaña):<br>I am the author of this document | Enviado: 14-ene.-2022 \| 21:00<br>Visto: 14-ene.-2022 \| 21:01<br>Firmado: 14-ene.-2022 \| 21:01 |
| **Información sobre confidencialidad de registros y firmas electrónicos:**<br>No ofrecido a través de DocuSign | | |
| Richard Polisson<br>richard.polisson@gmail.com<br>Nivel de seguridad: Correo electrónico, Autenticación de cuenta (obligatoria) |  <br>DocuSigned by:<br>Richard Polisson<br>Signer Name: Richard Polisson<br>Signing Reason: I approve this document<br>Signing Time: 14-Jan-2022 \| 14:28 PST<br>5D68449A7A484F37B1A3BF32A012FA7E<br>Adopción de firma: Estilo preseleccionado<br>Identificador de firma: 5D68449A-7A48-4F37-B1A3-BF32A012FA7E<br>Utilizando dirección IP: 98.216.179.240<br>Con autenticación de firma a través de la contraseña de DocuSign<br>Con motivos de la firma (en cada pestaña):<br>I approve this document | Enviado: 14-ene.-2022 \| 21:00<br>Visto: 14-ene.-2022 \| 22:27<br>Firmado: 14-ene.-2022 \| 22:28 |
| **Información sobre confidencialidad de registros y firmas electrónicos:**<br>Aceptado: 14-ene.-2022 \| 22:27<br>ID: a3463661-14c2-43e2-8f6f-2a3588081a71 | | |

| Eventos de firmante en persona | Firma | Fecha y hora |
|---|---|---|

| Eventos de entrega al editor | Estado | Fecha y hora |
|---|---|---|

| Eventos de entrega al agente | Estado | Fecha y hora |
|---|---|---|

| Eventos de entrega al intermediario | Estado | Fecha y hora |
|---|---|---|

| Eventos de entrega certificada | Estado | Fecha y hora |
|---|---|---|

| Eventos de copia de carbón | Estado | Fecha y hora |
|---|---|---|

| Eventos del testigo | Firma | Fecha y hora |
|---|---|---|

| Eventos de notario | Firma | Fecha y hora |
|---|---|---|

| Eventos de resumen de sobre | Estado | Marcas de tiempo |
|---|---|---|
| Sobre enviado | Con hash/cifrado | 14-ene.-2022 \| 21:00 |
| Certificado entregado | Seguridad comprobada | 14-ene.-2022 \| 22:27 |
| Firma completa | Seguridad comprobada | 14-ene.-2022 \| 22:28 |
| Completado | Seguridad comprobada | 17-ene.-2022 \| 09:05 |

| Eventos del pago | Estado | Marcas de tiempo |
|---|---|---|

**Información sobre confidencialidad de registros y firmas electrónicos**

## ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, Orion Clinical Services Limited (acting for itself and on behalf of its Affiliates) - Part 11 (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

### Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

### Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

### Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

### All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

**How to contact Orion Clinical Services Limited (acting for itself and on behalf of its Affiliates) - Part 11:**

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: jim.kendall@simbecorion.com

**To advise Orion Clinical Services Limited (acting for itself and on behalf of its Affiliates) - Part 11 of your new email address**

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at jim.kendall@simbecorion.com and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

**To request paper copies from Orion Clinical Services Limited (acting for itself and on behalf of its Affiliates) - Part 11**

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to jim.kendall@simbecorion.com and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

**To withdraw your consent with Orion Clinical Services Limited (acting for itself and on behalf of its Affiliates) - Part 11**

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to jim.kendall@simbecorion.com and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

**Required hardware and software**

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

**Acknowledging your access and consent to receive and sign documents electronically**

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify Orion Clinical Services Limited (acting for itself and on behalf of its Affiliates) - Part 11 as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by Orion Clinical Services Limited (acting for itself and on behalf of its Affiliates) - Part 11 during the course of your relationship with Orion Clinical Services Limited (acting for itself and on behalf of its Affiliates) - Part 11.