Protocol Title:	Pharmacokinetic Study Comparing MB05 (Proposed Palivizumab Biosimilar), EU-sourced Synagis® and US-sourced Synagis® in Healthy Volunteers.
NCT Number:	NCT05121246
Statistical Analysis Plan version date:	Version 2.0, 15 June 2023

STATISTICAL ANALYSIS PLAN

FANTASY–A RANDOMISED, DOUBLE-BLIND, 3-ARM PARALLEL STUDY TO COMPARE THE PHARMACOKINETICS, SAFETY, IMMUNOGENICITY AND TOLERABILITY OF MB05 (PROPOSED PALIVIZUMAB BIOSIMILAR), EU-SOURCED SYNAGIS® AND US-SOURCED SYNAGIS®, ADMINISTERED AS A SINGLE DOSE INTRAMUSCULAR INJECTION IN HEALTHY VOLUNTEERS.

Protocol No.: MB05-A-01-21

Sponsor Name and Address:	mAbxience Research S.L. [redacted]-Spain
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Table of Contents

List of Abbreviations

Abbreviation	Description
ADA	Anti-drug Antibody
ADR	Adverse Drug Reaction
AEs	Adverse Events
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Class
AUC0-inf	Area Under the Concentration-Time Curve From 0 to Infinity
AUC0-last	Area Under the Concentration-Time Curve From 0 to Time of Last Quantifiable Concentration
BLQ	Below The Limit of Quantifiable
BMI	Body Mass Index
CL/F	Total Apparent Body Clearance
Cmax	Maximum Observed Concentration
CS	Clinically Significant
CSR	Clinical Study Report
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eCRFs	Electronic Case Report Forms
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
HDL	High-Density Lipoprotein
IAS	Immunogenicity Analysis Set
ID	Identification
IM	Intramuscular Injection
INR	International Normalized Ratio
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not Clinically Significant
PK	Pharmacokinetics
PKS	Pharmacokinetic Analysis Set
PT	Preferred Terms
PT	Prothrombin Time
SAEs	Serious Adverse Events
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class
SOPs	Standard Operating Procedures

SS	Safety Analysis Set
t1/2	Apparent Terminal Elimination Half-Life
TEAEs	Treatment Emergent Adverse Events
TFLs	Tables, Listings, And Figures
Tmax	Time To Cmax
TT	Thrombin time
UN	Unknown
Vz/F	Apparent Volume of Distribution
WBC	White Blood Cells
WHO-DD	World Health Organization Drug Dictionary
λz	Terminal Elimination Rate Constant

1 INTRODUCTION

This Statistical Analysis Plan (SAP) provides the outline for the statistical analysis of the data collected for MB05-A-01-21 titled: "FANTASY–A Randomised, Double-Blind, 3-arm Parallel Study to Compare the Pharmacokinetics, Safety, Immunogenicity and Tolerability of MB05 (Proposed Palivizumab Biosimilar), EU-sourced Synagis® and US-sourced Synagis®, Administered as a Single Dose Intramuscular Injection in Healthy Volunteers." (Version 2.0 dated 07 June 2022).

This SAP is written with consideration of the recommendations outlined in the International Council for Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports.

The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock, reasons for such deviations, and all alternatives or additional statistical analyses that may be performed will be described the Clinical Study Report (CSR).

If the SAP differs the statistical considerations in the protocol, details will be given in section 18.

Summary of Changes

Statistical analysis plan version 1.0 was approved and executed on 29-Nov-2022. This SAP Version 2.0, 15-Jun-2023 was prepared to include a pharmacokinetic (PK) sensitivity analysis and to remove the analysis of neutralising antibody assessments from the analysis plan following sponsor confirmation that this test will no longer be performed. Section 5.2 pharmacokinetic analysis set definition was updated to add the criteria to include subjects "who received any amount of study treatment". Section 14.8 was updated to include listings and summaries of body mass index (BMI). Additionally, the lead statistician for this study has changed to Paul Stevenson, and the PK signatory is Oriol Peris Serrano, and the sponsor medical monitor has changed to Andrea Espiragares. Avance Clinical's address was also updated.

2 PROJECT OVERVIEW

2.1 Description of Study Design

This is a multicentre, randomised, double-blind, 3-arm parallel group study.

Up to a total of 141 participants are planned to be enrolled and randomised to receive a single dose of MB05, EU-Synagis® or US-Synagis with participants randomised to Arm A, B or C in equal proportions (1:1:1). Participants will be enrolled across multiple sites in Australia and New Zealand.

In Group 1, a total of 9 participants will be enrolled and dosed with 3 mg/kg MB05, 3 mg/kg EU-Synagis® or 3 mg/kg US-Synagis® (1:1:1). Once all participants in Group 1 have completed the Day 8 visit, a safety review committee (SRC) will meet to review all available safety data from Group 1, up to and including Day 8. No additional enrolment or dosing of the remaining participants should occur until the safety review is complete.

Following approval by the SRC, Group 2 may be enrolled (n=132, randomised 1:1:1 MB05: EU-Synagis®: US-Synagis®).

2.2 Objectives

2.2.1 Primary Objectives and Endpoints

The primary objective of this study is:

- To establish the bioequivalence between MB05 and EU-Synagis®, between MB05 and US-Synagis® and between EU-Synagis® and US-Synagis® up to Day 99, in terms of:
    - Area under the serum concentration versus time curve from time zero to infinity ($AUC_{0\text{-}inf}$)
    - Maximum observed serum concentration (C_{max})

The primary endpoint of this study is:

- Bioequivalence between MB05 and EU-Synagis®, between MB05 and US-Synagis® and between EU-Synagis® and US-Synagis® will be determined for $AUC_{0\text{-}inf}$ and C_{max}

2.2.2 Secondary Objectives and Endpoints

The secondary objectives of this study are:

- To compare the pharmacokinetics (PK) of MB05 with EU- Synagis® and US-Synagis® following a single 3 mg/kg intramuscular injection (IM) injection in healthy adult volunteers.
- To assess the safety and tolerability of MB05, EU- Synagis® and US-Synagis®
- To assess the immunogenicity of MB05, EU- Synagis® and US-Synagis®

The secondary endpoints of this study are:

- Additional PK parameters to be determined include (but are no limited to):
    - Time to C_{max} (T_{max})
    - Apparent terminal elimination half-life ($t_{1/2}$)
    - Apparent total serum clearance (CL/F)
    - Apparent volume of distribution (Vz/F)

- Area under the concentration-time curve from 0 to time of time t (AUC_t)

- Safety and tolerability endpoints include:
  - Incidence, type, and severity of Adverse events (AEs)
  - Changes from baseline in clinical laboratory results (haematology, serum chemistry, coagulation, and urinalysis)
  - Changes from baseline in vital signs parameters
  - Changes from baseline in physical examination findings
  - Change from baseline in body weight
  - Change from baseline in ECG parameters
  - Incidence, type and severity of injection site reactions
- Immunogenicity endpoints include:
  - Incidence of anti-drug antibody (ADA) against MB05, US- and EU-Synagis®, including titres for ADA

3 SAMPLE SIZE

Up to a total number of 141 healthy subjects (male and female) are planned to be enrolled in the study. Subjects who meet the entry criteria will be randomised to receive a single dose of MB05, EU-sourced Synagis® or US-sourced Synagis® in a 1:1:1 fashion.

The reported coefficients of variation (CVs) for AUC and Cmax for Synagis® vary between 0.25 and 0.35. Based on a worst-case CV of 0.35 (Robbie et al., 2012), alpha of 0.05 (i.e., utilising a two-sided 90% CI around the mean difference) and a true hypothesised ratio for the mean difference of 1, a total of 135 subjects (45 subjects per arm respectively), 1:1:1 ratio) will provide approximately 85% power to demonstrate bioequivalence of MB05 with EU-sourced Synagis® and US-sourced Synagis®. Assuming a 5% dropout, a total of 141 subjects (47 subjects per arm) are sufficient for this measure.

4 STATISTICAL CONSIDERATIONS

4.1 Standard Operating Procedures and Software

Data will be handled and processed per the sponsor representative's (Avance) Standard Operating Procedures (SOPs), which are written based on the principles of Good Clinical Practice (GCP).

All data conversions and statistical analyses will be performed using SAS® Version 9.4 or higher (SAS Institute, Cary, North Carolina, USA) with program code prepared specifically for the study by qualified Avance statisticians and SAS® programmers.

4.2 General Considerations

All data collected during the study (data originating from the electronic Case Report Forms (eCRFs) or electronic transfers will be presented in the data listings. Event-based listings will be sorted by treatment arm, participant identification and event start date/time (i.e., AE start date/time). Assessment-based listings will be sorted by treatment arm, parameter name (alphabetically unless specifically stated otherwise), participant identification, visit and time point (if applicable).

Unless otherwise stated, the following methods will be applied:

- Continuous variables: Descriptive statistics will include the number of non-missing values (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum values.

  The minimum and maximum values will be displayed to the same decimal precision as the source data, the arithmetic mean and median values will be displayed to one more decimal than the source data, and the SD values will be displayed to two more decimals than the source data for the specific variable.

  The appropriate precision for derived variables will be determined based on the precision of the data on which the derivations are based, and statistics will be presented in accordance with the abovementioned rules.

- Categorical variables: Descriptive statistics will include frequencies and percentages per category. The denominator in all percentage calculations will be the number of Participants in the relevant analysis population with non-missing data, unless specifically stated otherwise. Percentages will be rounded to one decimal place and will not be displayed for zero frequencies.

- Presentation of p-values and confidence intervals: 90% confidence intervals will be computed, and reported to four significant figures, p-values will be displayed up to three decimal places and as "<0.001" if the value is below 0.001.

- Repeat/unscheduled assessments: Only values collected at scheduled study visits/time points will be presented in summary tables. If a repeat assessment was performed, the result from the original assessment will be presented as the result at the specific visit/time point. All collected data will be included in the data listings. If an unscheduled visit was intended to replace the missing assessment for a scheduled visit this should be documented clearly before values are carried forward as a scheduled visit assessment.

- Assessment windows: All assessments will be included in the data listings and the protocol specified visit windows will not be applied to exclude assessments that were

not performed on the protocol specified visit days. Protocol visit windows will be as per CRF data collection.

- Result display convention: Results will be centre aligned in all summary tables and listings. Participant identification, visit, and parameter labels and comments may be left aligned if required.
- Conversion of categorical values: In some instance, continuous variables may be expressed as a range (i.e., < 9). The original source data captured will be displayed in data listing (i.e., <9), while values may be converted to another number for summary table purposes and the calculation of change from baseline values. As an example, a value of < 9 may be converted to one significant figure less as 8.
- Date and time display conventions: The following display conventions will be applied in all outputs where dates and/or times are displayed:
    - Date only: YYYY-MM-DD
    - Date and time: YYYY-MM-DD/HH:MM

If only partial information is available, unknown components of the date or time will be presented as UN (Unknown), for example "2022-UN-UN" or "UN:UN" for time.

4.3 Key Definitions

The following definitions will be used:

- Date of the First Study Treatment Administration: The date of the first study treatment administration is defined as the earliest date on which a study treatment was administered.
- Baseline: The Baseline value is defined as the last available valid, non-missing observation for each Participant prior to first study treatment administration on Day 1. Repeat and unscheduled assessments will be included in the derivation of the Baseline values only if Baseline value is missing.
- Change from Baseline: The change from Baseline value is defined as the difference between the result collected/derived at a particular visit and the Baseline value.

  The change from Baseline value at each visit will be calculated for all continuous parameters using the following formula:

  Change from Baseline Value = Result at specified visit – Baseline Value

  The change from Baseline value will only be calculated if the specific visit result and the Baseline value for the parameter are both available and will be treated as missing otherwise.

- Study Day: The study day of an event is defined as the relative day of the event starting with the date of the first study treatment administration (reference date) as Day 1 (there will be no Day 0).

  The study day of events occurring before the first study treatment administration will be calculated as:

  Study Day = (Date of Event - Date of First Study Treatment Administration)

  For events occurring on or after Day 1, study day will be calculated as:

Study Day = (Date of Event - Date of First Study Treatment Administration) + 1

Study days will only be calculated for events with complete dates and will be undefined for events that are 'Ongoing' at the end of the study.

- Actual Time from First Dose (hours) in PK related outputs is defined as:

  (Date/Time of PK Sample collection) – (Date/Start Time of First Dose on Day 1).

- Actual Time Deviation (hours) in PK related outputs is defined as:

  (Actual PK Sample Collection Time Post Dose) – (Scheduled PK Sample Collection Time Post Dose).

- AE Duration: Adverse event duration (in days, to two decimal places), calculated as

  (Resolution Date + Resolution Time) – (Onset Date + Onset Time)

  AE duration will only be calculated for events with complete dates/times and will be undefined for events that are 'Ongoing' at the end of the study.

4.4 Multiple Comparisons and Multiplicity

No multiplicity adjustment will be carried out for this study.

4.5 Handling of Missing Data

In general, all data will be analysed as collected and missing values will not be imputed or replaced unless stated otherwise.

4.6 Treatment Group and Visit Display Conventions

Summary Table:

In summary table, the representation as below:

- Arm A: 3 mg/kg MB05
- Arm B: 3 mg/kg EU-Synagis®
- Arm C: 3 mg/kg US-Synagis®
- Overall

Data Listing:

In data listing, the following labels will be used:

- Arm A: 3 mg/kg MB05
- Arm B: 3 mg/kg EU-Synagis®
- Arm C: 3 mg/kg US-Synagis®

Visit labels:

The following visit labels will be used:

- Screening (Listing only)
- Day -1 (Listing only)
- Baseline (Table only)
- Day 1

- Day 2
- Day 3
- Day 4
- Day 5
- Day 6
- Day 8
- Day 15
- Day 22
- Day 29
- Day 36
- Day 43
- Day 57
- Day 71
- Day 85
- End of Study
- Early Termination (Listing only)
- Unscheduled (Listing only)

For listings, these labels will be used, with visit representing baseline (either screening/baseline or unscheduled visit marked as "[1]" with a footnote indicating it is baseline value). These visit displays will be sorted by date of visit within each Participant:

5 ANALYSIS POPULATIONS

5.1 Safety Analysis Set (SS)

The Safety Analysis Set will be defined as all randomized participants who received any amount of study treatment and will be based on the actual treatment received, if this differs from that to which the participant was randomized to. The Safety Analysis Set will be used for the summaries of all safety, baseline, and demographic data.

5.2 Pharmacokinetic Analysis Set (PKS)

The Pharmacokinetic Analysis Set will be defined as all randomized participants who received any amount of study treatment and where there is sufficient data for reliable estimates of C_{max} (as determined by the study Pharmacokineticist).

5.3 Per Protocol Pharmacokinetic Analysis Set

The per protocol pharmacokinetic analysis set will include all subjects in the PK Analysis Set who have no major protocol violations that impact on pharmacokinetics. Subjects who do not complete the sampling per schedule but have sufficient data points to construct each concentration-time profile will be considered PK evaluable.

5.4 Immunogenicity Analysis Set (IAS)

The Immunogenicity Analysis Set will be defined as all randomized participants who receive any amount of study treatment and who have at least 1 evaluable immunogenicity parameter post-dose and will be summarized according to the treatment actually received, if this differs from that to which the participant was randomized. The immunogenicity Analysis Set will be used for the summaries of all immunogenicity data.

6 PARTICIPANT DISPOSITION

The following participant disposition information will be reported:

Summary of Disposition:

- Number of Participants Completed
- Number of Participants Not Completed
- Reason for Non-Completion (percentage denominator based on number of withdrawn Participants)

Counts and percentages will be reported for summary of disposition and will be provided using the Safety Analysis Set for treatment groups defined in Section 4.6.

Listings will be provided for summary of disposition along with the date of study completion/discontinuation and the primary reason for non-completion. The listing will be provided by treatment groups (Section 4.6) sorted by Participant Identification (ID) for the Safety Analysis Set.

7 ANALYSIS SET

The following analysis set information will be reported:

- Participants included in Safety Analysis Set
- Participants included in Pharmacokinetic Analysis Set
- Participants included in Per Protocol Pharmacokinetic Analysis Set
- Participants included in Immunogenicity Analysis Set

Counts and percentages for these participants under different population sets will be provided using the Safety Analysis Set for treatment groups defined in Section 4.6.

Listings will be provided by treatment groups (Section 4.6) sorted by Participant ID for the Safety Analysis Set.

8 PROTOCOL DEVIATIONS

The following protocol deviations, but not be limited will be reported:

- Inclusion/Exclusion Criteria – participant enrolled without meeting eligibility criteria.
- Laboratory – deviations in lab sample processing, storage or shipment, or lab kits/supplies.
- Visit Schedule visit window deviations, missed study visits.
- IP Dosing and/or Accountability – participant received wrong treatment dosed outside of the protocol timepoints or received treatment not stored per protocol.
- Concomitant Medication – participant received medication prohibited by the protocol.
- Study Procedure/Tests – assessment window deviations, missed study assessments, incorrect order of assessments, assessments not conducted per protocol.
- Randomisation
- Safety Reporting (AEs/SAEs) – SAEs not reported within the expected turn-around-time per regulatory reporting requirements (i.e., 24 hours from awareness). Pregnancy not reported within the expected turn-around time per regulatory reporting requirements (i.e., 24 hours from awareness).
- Protocol Discontinuation Criteria – participant remained on the study after meeting protocol withdrawal criteria.
- Informed Consent – any informed consent issues, including Participant not consented prior to study assessments/procedures commencing, new clinical study procedures performed before participant was re-consented, initial consent not signed/dated/ initialled per local regulatory guidelines.
- Data Protection and Privacy
- Participant Compliance – compliance issues with study requirements including diet and physical activity restrictions, study visit attendance.

All protocol deviations will be assessed between Avance and the Sponsor during study before database lock and unblinding.

The number of participants with at least one protocol deviations, and the category of protocol deviations will be summarized in accordance with Section 4.2 using the Safety Analysis Set for treatment groups defined in Section 4.6.

Listing of all protocol deviations will be provided by treatment group (Section 4.6) sorted by Participant ID for the Safety Set A separate protocol deviation listing will be created for the Pharmacokinetic Analysis Set.

In addition, all available data collected in General Common Forms originating from the electronic Case Report Forms (eCRFs) will be provided in data listing by treatment groups (defined in Section 4.6) sorted by Participant ID for the Safety Set.

9 DEMOGRAPHICS AND BASELINE INFORMATION

The demographics variables to be reported are listed below:

- Age (years) at baseline
- Sex
- Women of child-bearing potential
- Race
- Ethnicity
- Height (cm) at baseline
- Weight (kg) at baseline
- BMI (kg/m^2) at baseline

These variables will be summarized using descriptive statistics in accordance with Section 4.2 under the Safety Analysis Set for treatment groups defined in Section 4.6. Demographics variables will also be listed by treatment groups (Section 4.6) under the Safety analysis Set sorted by Participant ID.

The following baseline information analysis will be listed by treatment groups (Section 4.6) under the Safety analysis Set sorted by Participant ID.

- Urine Drug Screen
- Alcohol Breath Test
- Serology
- COVID-19 Test

10 MEDICAL HISTORY

Medical history conditions will be coded using the version 25.0 of the Medical Dictionary for Regulatory Activities (MedDRA) that is available at the time of study commencement. Terms will be coded to the full MedDRA hierarchy, but the system organ class (SOC) and preferred terms (PT) will be of primary interest for the analysis. Where SOC and PT are reported, the display will be sorted by the descending order by SOC and then by PT in the Overall treatment group.

Medical history listings will be provided by treatment groups (Section 4.6) sorted by Participant ID for the Safety Analysis Set, along with start date, end date/ongoing status of medical history.

11 PRIOR AND CONCOMITANT MEDICATION

Prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHO-DD) (the version of WHODRUG GLOBAL B3 March 2022).

- Prior Medications: Prior medications are defined as any medication where the use was stopped prior to the first administration of the study medication.
- Concomitant Medications: Concomitant medications are defined as medications (other than the study drug) taken at least once after the start of first study drug administration.

  Medications stopped prior to the day of first study drug administration will not be considered concomitant medications, but they will be coded by WHO-DD and listed. If a clear determination cannot be made as to whether the medication is concomitant or not due to missing or incomplete data, the medication will be treated as concomitant medication taken during the study.

The number and percentage of Participants using at least one concomitant medication will be displayed together with the number and percentage of Participants using at least one medication within each anatomical therapeutic class (ATC-Level 2) and preferred name. These will be summarized under the Safety Analysis Set for treatment groups defined in Section 4.6. Where ATC-Level 2 and preferred name are reported, the display will be sorted by the descending order by ATC-Level 2 and then by PT in the Overall treatment group.

Listing of full details of prior and concomitant medications (medication taken, therapeutic class, start and stop dates/ongoing status, indication, routes, frequency, and dosage) will be provided by treatment group (Section 4.6) sorted by Participant ID and start date for the Safety Analysis Set.

12 TREATMENT AND EXPOSURE

All study drug administration information (study drug administered [Yes/No], reason not administered, date and time (start time/end time) of administration, location, route, total dose [mg]/total volume [mL], dose interruption, reason for dose interruption, start time of interruption, volume administered prior to interruption, dose restarted, following the protocol, reason for not following the protocol, and entire volume not administered) will be listed by treatment group (Section 4.6) sorted by Participant ID and visit for the Safety Analysis Set.

13 EFFICACY

No efficacy analysis is planned for this study.

14 SAFETY

All safety endpoints will be analyzed using the safety analysis set.

14.1 Adverse Events

AE verbatim terms will be coded using the version 25.0 of the Medical Dictionary for Regulatory Activities (MedDRA). AEs and SAEs are defined in the study protocol.

- Treatment Emergent Adverse Events (TEAEs) are defined as adverse events that occurred or worsened from the first administration of study drug. If determination cannot be made as to whether the event is treatment emergent due to missing or incomplete data, the adverse event will be treated as treatment emergent.
- Treatment-Related are defined as any TEAEs reported with the causality of "Possibly", "Probably", "Definitely" to study treatment.

All AE summaries will be restricted to TEAEs only.

The TEAE summaries will include:

- Overall Summary of TEAEs
    - TEAEs
    - Treatment Related TEAEs
    - Serious TEAEs
    - Serious Treatment Related TEAEs
    - TEAEs leading to death
    - TEAEs leading to study withdrawal

The following table summaries will be presented by SOC and PT by treatment groups defined in Section 4.6:

- TEAE summary by SOC and PT
- TEAE summary by SOC, PT and Severity
- TEAE summary by SOC, PT and relationship (study treatment)
- Serious TEAE summary by SOC and PT
- Treatment Related TEAE summary by SOC and PT
- Serious Treatment-Related TEAE summary by SOC and PT
- Treatment Related TEAE summary by SOC, PT and Severity
- TEAE summary if events leading to study withdrawal by SOC and PT

The above items will be presented using summary tables, which will include the number of participants (%) experiencing an event and the number of events and the number of events. If a Participant experienced the same adverse event multiple times, this will only be counted once for the purpose of counting the number of Participants experiencing that adverse event. Summary tables will be done for the Safety Analysis Set for treatment groups defined in Section 4.6. Where SOC and PT are reported, the display will be sorted by the descending order by SOC and then by PT in the Overall treatment group.

All AEs will be listed and will include the verbatim term, SOC, PT, SAE, start/end date/time, causality/severity, relationship to study treatment, relationship to procedure of injection, outcome, action taken, and study withdrawal. A separate listing will be created for SAEs. These listings will be presented by treatment groups (Section 4.6) sorted by Participant ID and AE start date for the Safety Analysis Set, along with age, sex, race, and baseline weight of the Participant.

14.2 Safety Laboratory Assessments

The following laboratory measurements will be taken at the time points specified in the study procedure schedule (Section 20):

- Haematology: Haemoglobin, Haematocrit, Thrombocyte count (platelets), Reticulocyte count, White blood cells (WBC) count with differential: Neutrophil count, Eosinophil count, Basophil count, Lymphocyte count, and Monocyte count
- Coagulation: Prothrombin time (PT), International normalized ratio (INR), Activated partial thromboplastin time (aPTT) and Thrombin time (TT)/thrombin clotting time (TCT).
- Chemistry: Sodium, Potassium, Chloride, Bicarbonate, Phosphate, Calcium, Glucose, Amylase, Lipase, Uric acid, Albumin, Protein, Lactate dehydrogenase (LDH), Creatine kinase, Creatinine or creatinine clearance (Cockroft/Gault), Urea, Alkaline phosphatase (ALP), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Gamma Glutamyl Transferase (GGT), Total bilirubin (total and direct), Total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), Triglycerides, Magnesium
- Urinalysis and Urine Microscopy: pH, Specific gravity, Glucose, Protein, Ketones, Bilirubin, Blood, Nitrite, Urobilinogen, Leukocyte esterase

For the haematology, coagulation, chemistry, continuous data summary statistics (as described in Section 4.2) will be presented for values and change from baseline value at each scheduled post baseline visit.

In addition, Shift tables from Baseline at each visit for haematology, coagulation, and chemistry lab parameters (low, normal, and high) will also be presented using counts and percentages.

For urinalysis, the urinalysis table will present counts and percentages of normal, abnormal clinically significant and non-clinically significant for the reported results at baseline and each post baseline visit for all parameters (as described in Section 4.2)

These summary tables will be based on the Safety Analysis Set for treatment groups defined in Section 4.6.

The listings of laboratory parameters (haematology, coagulation, chemistry, and urinalysis) will include all the information collected. In addition, the observations that are used as the baseline record (value) for each parameter will be flagged, and the change from baseline values (where applicable) at each scheduled post baseline (scheduled and unscheduled) visit will be presented. A separate listing for individual subject profiles to include any laboratory parameters with at least one post-dose value outside the laboratory's reference ranges will be presented. These listings will be presented by treatment groups (Section 4.6) sorted by Participant ID and visit for the Safety Analysis Set, along with age, sex, race, and baseline weight of the Participant.

14.3 Vital Sign Assessments

The following vital signs measurements will be taken at the time points specified in the study procedure schedule (section 20):

- Systolic blood pressure (SBP) (mmHg)
- Diastolic blood pressure (DBP) (mmHg)
- Pulse Rate (beats/min)
- Respiratory rate (breaths/min)
- Body Temperature (ºC)
- Overall Clinical Interpretation:
    - Normal
    - Abnormal NCS (Not Clinically Significant)
    - Abnormal CS (Clinically Significant)

The parameter names that will be used in the outputs will comprise of the test name and the unit of measure, for example, 'Systolic Blood Pressure (mmHg)'. Parameters will be sorted in the order that the measurements were collected in on the Vital Signs eCRF page within the tables and listings.

Summary statistics for vital sign parameters in accordance to Section 4.2 will be presented for baseline and for each scheduled post-baseline visit (which also includes change from baseline). In addition, overall clinical interpretation result (Normal, Abnormal not clinically significant, Abnormal and clinically significant,) will be summarized by counts and percentages for baseline and for each scheduled post baseline visit. These summary tables will be done for the Safety Analysis Set for treatment groups defined in Section 4.6.

The listing of vital sign parameters will include all the information collected. In addition, the observations that are used as the baseline record (value) for each parameter will be flagged, and the change from baseline values at each post baseline (scheduled and unscheduled) visit will be presented. This listing will be presented by treatment groups (Section 4.6) sorted by Participant ID and visit for the Safety Analysis Set, along with age, sex, race, and baseline weight of the Participant.

14.4 12-Lead Electrocardiogram (ECG)

The following ECG measurements will be taken at the time points specified in the study procedure schedule (Section 20):

- Heart Rate (bpm)
- QT interval (msec)

- PR interval (msec)
- QRS duration (msec)
- QTcF (msec)
- Overall ECG clinical interpretation
  - Normal
  - Abnormal NCS (Not Clinically Significant)
  - Abnormal CS (Clinically Significant)

The parameter names that will be used in the outputs will comprise of the test name and the unit of measure, for example, 'Heart Rate (beats/min)'. Parameters will be sorted in the order that the measurements were collected in on the ECG eCRF page within the tables and listings.

For ECG triplicates, the mean of ECG triplicated, and the worst clinical interpretation will be taken as the ECG values for each participant at applicable visit.

Summary statistics for ECG parameters in accordance with Section 4.2 will be presented for baseline and for each scheduled post baseline visit (which also includes the change from baseline). In addition, overall ECG clinical interpretation result (Normal, Abnormal not clinically significant, and Abnormal clinically significant) will be summarized by counts and percentages for baseline and for each scheduled post baseline visit. These summary tables will be done for the Safety Analysis Set for treatment groups defined in Section 4.6.

The listing of ECG parameters will include all the information collected. In addition, the observations that are used as the baseline record (value) for each parameter will be flagged, and the change from baseline values at each post baseline (scheduled and unscheduled) visit will be presented. This listing will be presented by treatment group (Section 4.6) sorted by Participant ID and visit for the Safety Analysis Set, along with age, sex, race, and baseline weight of the Participant.

14.5 Physical Examinations

The listing of physical examinations (including full and symptom directed examinations) will include all the information collected. This listing will be presented by treatment group defined in Section 4.6, sorted by Participant ID and visit for the Safety Analysis Set.

14.6 Pregnancy Test and Follicle Stimulating Hormone Test

The listing of pregnancy test (urine and serum based) and FSH test (post-menopausal females only) will include all the information collected. This listing will be presented by treatment group defined in Section 4.6, sorted by Participant ID and visit for the Safety Analysis Set.

14.7 Injection Site Reaction

The following Injection Site Reaction measurements will be taken at the time points specified in the study procedure schedule (Section 20):

- Pain
- Tenderness
- Erythema/Redness
- Induration/Swelling

Parameters will be sorted in the order that the measurements were collected in on the Injection Site Reaction eCRF page within the tables and listings.

The severity of the injection site reaction parameters will be summarized by counts and percentage for baseline and for each scheduled post-baseline visits. These summary tables will be done for the Safety Analysis Set for treatment groups defined in Section 4.6.

The listing of injection site reaction parameters will include all the information collected. In addition, the observations that are used as the baseline record for each parameter will be flagged, and date/time of assessment, location, and other reaction at injection site (Yes/No) will be presented. This listing will be presented by treatment groups (Section 4.6) sorted by Participant ID and visit for the Safety Analysis Set.

14.8 Body Weight and Body Mass Index

The listing of body weight assessment and BMI will include all the information collected. This listing will be presented by treatment group defined in Section 4.6, sorted by Participant ID and visit for the Safety Analysis Set.

Summary statistics for body weight and BMI in accordance with Section 4.2 will be presented for baseline and for each scheduled post baseline visit (which also includes the change from baseline). The summary table will be done for the Safety Analysis Set for treatment groups defined in Section 4.6.

The value of BMI that is recorded in the electronic data capture system will be sued for all listings and summary tables. BMI to be calculated using the height value recorded at screening.

15 PHARMACOKINETICS

All PK analyses will be conducted on the plasma concentration data of palivizumab.

The individual subject listings of PK plasma concentrations will be presented for the Safety Analysis Set to include data for placebo subjects, while the summary of plasma concentrations will be based on the PK Analysis Set.

Individual and mean PK parameters and any outputs related to PK parameters (e.g., bioequivalence analysis) will be based on the Per Protocol PK Analysis Set.

Individual plasma concentration over time plots in linear and logarithmic scale will be presented for Full PK Analysis population. Mean plasma concentration over time plots will be presented for Per-protocol PK population.

15.1 Data Handing for PK Data

Plasma concentration values not collected or not determined will be treated as missing. The plasma concentrations that are below the limit of quantifiable (BLQ) will be designated a value of zero for the summary of concentration-time data, except for geometric mean, where they will be excluded from the calculation.

For individual and mean plasma concentration-time plots, BLQ values will be set to zero for linear plots and BLQ values will be excluded from presentation semi-logarithmic scale.

15.2 Summary Statistics for Plasma PK Concentration Data

Plasma concentrations of palivizumab will be used as supplied by the laboratory. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the laboratory.

The actual sampling date and time and elapsed time relative to dosing time for plasma data will be listed by Participant and nominal sampling time, with time deviation (difference in hours between nominal and actual sampling times) calculated. These results will also be listed by treatment group (Section 4.6), sorted by Participant ID and visit.

Summary statistics of PK concentration data of palivizumab (number of non-missing observation [n], arithmetic mean, standard deviation [SD], coefficient of variation [CV%], geometric mean, median, minimum and maximum) will be calculated for each time point and summarised by treatment group (Section 4.6).

When reporting individual values and descriptive statistics for palivizumab concentration data, the following rules will apply regarding rounding and precision:

- Descriptive statistics for PK concentration data will be reported to the same level of precision as the individual data for the minimum and maximum, and to 1 additional decimal place or 1 additional significant figure – depending on the reporting format of the original data with a maximum of 3 significant figures - for the mean (arithmetic and geometric), median and standard deviation.
- Between-Participant CV% will be reported as a percentage to 1 decimal place.

15.3 Summary Statistics for Plasma PK Parameter

Calculated PK parameters will be listed and summarized descriptively, including number of non-missing observation (n), arithmetic mean, SD, minimum, median, maximum, coefficient of variation [CV(%)], geometric mean, geometric CV%.

When reporting individual values and descriptive statistics for PK plasma parameters data for palivizumab, the following rules will apply to rounding and precision:

- Individual values for PK parameters will be reported to 3 significant figures.
- Descriptive statistics for PK parameters will be reported to 3 significant figures.
- Between-Participant CV% and geometric CV% will be reported as a percentage to 1 decimal place.
- Missing data will not be imputed.

15.4 Concentration-Time Profiles

Individual plasma concentrations of palivizumab over actual time will be plotted with the concentration result (y-axis) displayed for the Full PK Analysis population on a linear scale and on a logarithmic scale.

Mean plasma concentrations of palivizumab over scheduled time will be plotted with the concentration result (y-axis) displayed for the Per-protocol PK Analysis population on a linear scale and on a logarithmic scale.

15.5 Plasma PK Parameters

For PK analysis, the PK samples from pre-dose to Day 99 will be considered. Actual sampling times will be used for the PK analysis, with the exception of pre-dose data which will be given the nominal time of 0.00 hr. If the actual sampling time is not recorded, the nominal sampling time will be used.

The plasma concentrations below the limit of quantifiable (BLQ) values will be treated as 0 for PK analysis.

The following PK parameters will, where possible be determined from the plasma concentration of palivizumab by non-compartmental analysis using Phoenix WinNonlin® software (version 8.3 or higher).

Parameter	Definition
C_{max}	Individual maximum concentration (C_{max}) values are directly determined from the plasma concentration time profiles for each Participant.
C_{29days}	Individual concentration values on Day 29±1 directly determined from the plasma concentration time profiles for each Participant.
C_{57days}	Individual concentration values on Day 57±3 directly determined from the plasma concentration time profiles for each Participant.
T_{max}	The time to attain maximum concentration. If the same C_{max} concentration occurs at different time points, T_{max} is assigned to the first occurrence of C_{max}.
$AUC_{0\text{-last}}$	The area under the curve spanning time interval from time zero to the last time point with measurable concentration using the linear trapezoidal rule.
$AUC_{0\text{-}168h}$	The area under the curve spanning time interval from time zero up to 168h post dose using the linear trapezoidal rule
AUC_{29days}	The area under the curve spanning time interval from time zero up to Day 29±1 post dose using the linear trapezoidal rule
AUC_{57days}	The area under the curve spanning time interval from time zero up to Day 57±3 post dose using the linear trapezoidal rule

$AUC_{0\text{-inf}}$	The area under the plasma concentration-time curve over the time interval from time 0 extrapolated to infinity (∞) using the following formula $AUC_{0-\infty} = AUC_{0-t} + \frac{C_t'}{\lambda_z}$ Where, C't is the predicted concentration at the time t (last time point with a measurable plasma concentration above the quantification limit) at which quantification was still possible, the calculation of λz or kel is given below.
$AUC_{\%extrap}$	The percentage of the AUC that has been extrapolated beyond the last observed data point, using the following formula $AUC_{\%extrap} = \left(\frac{AUC_{0-\infty} - AUC_{0-t}}{AUC_{0-\infty}}\right) * 100$
λz or K_{el}	The apparent terminal elimination rate constant will be estimated from a regression of ln(C) versus time over the terminal log-linear drug disposition portion of the concentration-time profiles.
$t_{½}$	The terminal half-life will be calculated from the terminal rate constant using the equation: $T_{1/2} = \frac{Ln(2)}{\lambda_z}$
CL/F	Apparent total plasma clearance will be calculated as following equation: $CL/F = \frac{D}{AUC_{0-\infty}}$ Where D = Administered dose; $AUC_{0-\infty} = AUC_{0\text{-inf}}$
V_z/F	Apparent terminal volume of distribution will be calculated according to the following equation: $V_z/F = \frac{CL/F}{\lambda_z}$

The following will be considered for reporting the PK parameters:

- The PK parameters which are not determined from PK analyses due to inadequate concentration data or missing data will be considered as 'not estimable (NE)'.
- No value of λ_z or Kel, CL/F and Vz/F, $AUC_{0\text{-inf}}$, and $t_{1/2}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile. Criteria which may indicate a failure to exhibit a terminal log-linear phase in the concentration-versus-time profile include:
  - Positive slope for log regression fit
  - $r^2_{adj} < 0.75$
  - Time points in the interval used in estimating the half-life span less than one half-life
  - Fewer than 3 points with measurable concentration after T_{max}
- Profiles which meet any of the above criteria will be reviewed on a case-by-case basis. Any variations from the above criteria will be noted as a comment in the data file of parameters.

15.6 Other Important PK Considerations

- If data permits, the other PK parameters may be reported.

- If T_{last} = T_{max}; C_{max} will not be reported for that Participant in the listings. It will be footnoted to indicate that sampling timepoints were not appropriate for that Participant.

15.7 Bioequivalence Analysis

The bioequivalence analysis will be conducted for C_{max}, $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}last}$. Additionally, the bioequivalence analysis will also be conducted for concentrations collected on Days 29±1 day and 57±3 days as well as for partial AUC up to 168 hours, Days 29±1 day and 57±3. Natural log-transformed PK parameter C_{max}, C_{29days}, C_{57days}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$, $AUC_{0\text{-}168h}$, and AUC up to Days 29 and 57 will be analysed using the general linear model with the treatment as fixed via PROC GLM in SAS. For the purpose of the analysis, a preliminary ANCOVA model including variables group, age, sex, BMI and weight will be performed. If variables age, sex, BMI or weight were to be significant in this analysis, these variables will be kept in the final analysis. Upon review of the immunogenicity analysis, secondary ANCOVA analysis including ADA as a categorical or numerical variable could be performed. The 90% confidence intervals of the geometric least square mean ratio of test and reference i.e., MB05 group means relative to the EU-Synagis group means will be obtained by back transformation.

The following comparisons will be done:

(1) MB05 as Test VS EU-Synagis® as Reference

(2) MB05 as Test VS US-Synagis® as Reference

(3) EU-Synagis® as Test VS US-Synagis® as Reference

Bioequivalence will be concluded for C_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$ and additional parameters C_{29days}, C_{57days} and partial areas $AUC_{0\text{-}168h}$, AUC_{29days} and AUC_{57days} between test and refence, if the 90% CIs for the ratio of geometric least squares means are contained within the range 80.00% to 125.00%. However, for C_{max}, a wider range 70.00% to 143.00% could also be considered.

16 PHARMACODYNAMICS

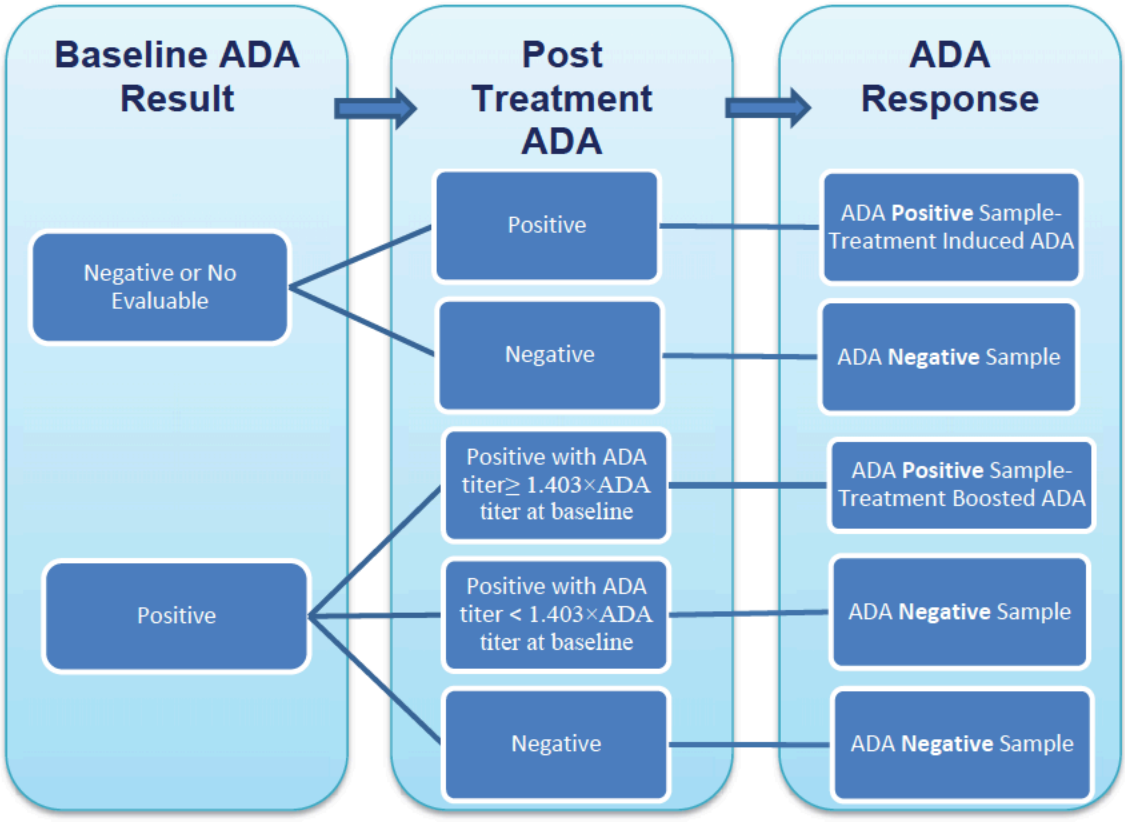
No pharmacodynamics analysis is planned for this study.

17 IMMUNOGENICITY

Anti-drug antibodies (ADA) to bevacizumab will be assessed at the time points specified by protocol.

ADA test methods enable characterization of samples into ADA positive vs. ADA negative. Each sample is categorized based on the following definitions:

- Baseline ADA positive: ADA is detected (ADA = positive) in the sample before initiation of treatment
- Baseline ADA negative: ADA is not detected (ADA = negative) in the sample before initiation of treatment or no evaluable ADA assessment (ADA result = missing) before initiation of treatment
- ADA positive sample: treatment induced, or treatment boosted ADA positive sample
    - Treatment induced ADA (TI-ADA) positive sample: After initiation of treatment, at least one ADA detected sample in a subject for whom ADA is not detected at baseline (ADA negative or no evaluable ADA assessment at baseline)
    - Treatment boosted ADA (TB-ADA) positive sample: After initiation of treatment, at least one ADA detected sample (ADA=positive) with ADA titer to be at least 1.403 times or greater than baseline positive titer (ADA titer >= 1.403 × ADA titer at baseline).
- ADA negative sample: After initiation of treatment, ADA not positive sample relative to baseline.



Subject ADA status is defined based on the sample ADA status as follows:

- Baseline ADA positive subject: A subject with baseline ADA positive sample
- Baseline ADA negative subject: A subject with baseline ADA negative sample or no evaluable ADA assessment at baseline
- ADA positive subject: A subject with at least one ADA positive sample relative to baseline at any time after initiation of treatment
- ADA negative subject: A subject with no ADA positive sample (no treatment induced, or treatment boosted) after initiation of treatment.

Immunogenicity data (ADA status [positive or negative] and titers (only applicable when ADA result is positive) will be listed by treatment group (Section 4.6) under the IAS, sorted by Participant ID and visit.

ADA status result will be summarized by counts and percentages of subjects testing positive for ADA for baseline (Day 1, pre dose) and for each scheduled post baseline visit. ADA titre data at each timepoint will be summarised using summary statistics.

Select analyses may be repeated for subsets with or without ADA and de novo ADA formation as appropriate including the association between PK parameters CL/F and AUC0-inf and TI-ADA status may be explored, as needed.

These summary tables will be done for the IAS for treatment groups defined in Section 4.6.

18 CHANGES TO THE PLANNED ANALYSIS

Not applicable.

19 INTERIM AND FINAL ANALYSIS

19.1 Interim Analysis

No formal interim analyses are planned for this study.

19.2 Final Analysis (End of Study)

The final analysis will be conducted after all Participants have completed the study, the clinical database has been locked, and the analysis populations have been approved prior to unblinding.

The final analysis will be based on the final version of the SAP. Any deviations from the planned analysis will be documented in the CSR.

20 APPENDIX 1 TIME AND EVENTS SCHEDULE

STUDY TIME SCHEDULE▼																				
STUDY PERIOD▶	Screen	Confinement					Follow-up													EOS/ETV
STUDY DAY▶	-28 to -2	-1	1			2	3	4	5	6	8	15	22	29	36	43	57	71	85	99
			Pre-dose	Dose	Post-dose															
VISIT WINDOW (± DAYS)												1	1	1	1	1	3	3	3	3
VISIT & FOLLOW-UP SCHEDULE▼																				
CLINIC CONFINEMENT▶		X																		
OUTPATIENT CLINIC VISIT▶	X						X	X	X	X	X	X	X	X	X	X	X	X	X	X
SCHEDULE OF ASSESSMENTS▼																				
Background Screening Assessments																				
Informed Consent	X																			
Eligibility Criteria	X	X [1]																		
Demographics	X																			
Medical History	X	X [1]																		
Height	X																			
Body Weight[2]	X	X																		X
Calculation of BMI [3]	X	X																		
Concomitant Medication Assessment [4]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test (Serum) [5]	X																			X
Pregnancy Test (Urine) [6]		X																		
Follicle-Stimulating Hormone [7]	X																			
Alcohol Breath or Urine Test [24]	X	X																		
Urine Drug Screen	X	X																		
Serology Screen [8]	X																			
COVID-19 Screening [9]	X																			
Safety and Tolerability Assessments																				
Adverse Events [10]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination (Full) [11]	X																			X

STUDY TIME SCHEDULE▼																				
STUDY PERIOD▶	Screen	Confinement					Follow-up													EOS/ETV
STUDY DAY▶	-28 to -2	-1	1			2	3	4	5	6	8	15	22	29	36	43	57	71	85	99
			Pre-dose	Dose	Post-dose															
VISIT WINDOW (± DAYS)												1	1	1	1	1	3	3	3	3
VISIT & FOLLOW-UP SCHEDULE▼																				
CLINIC CONFINEMENT▶		X																		
OUTPATIENT CLINIC VISIT▶	X						X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination (Symptom-directed) [12]		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs (BP, PR, RR, Temp) [13]	X	X	X		..X..	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG [14]	X	X	X		X															X
Clinical Laboratory Safety Tests (Blood) (Coagulation, Serum Chemistry, Haematology) [15]	X	X				X		X			X	X		X			X		X	X
Safety Laboratory Tests (Urinalysis) [16]	X	X				X		X			X	X								X
Injection Site Reaction Assessment [17]			X		..X..	X	X	X	X	X										X [23]
Pharmacokinetic, Pharmacodynamic and Immunogenicity Assessments																				
Blood sampling (PK) [18]			X		..X..	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sampling (ADA/nAb)) [19]			X									X		X			X			X
Other																				
Dose Administration [20]				X																
Randomisation [21]		X																		
Check-in		X																		
Check-out [22]						X														

21 REFERENCES

1) Clinical Study Protocol Version 2.0 dated 07 June 2021.

2) Robbie GJ, Zhao L, Mondick J, Losonsky G, Roskos LK. Population pharmacokinetics of palivizumab, a humanized anti-respiratory syncytial virus monoclonal antibody, in adults and children. Antimicrob Agents Chemother. 2012 Sep;56(9):4927-36. Erratum in: Antimicrob Agents Chemother. 2012 Oct;56(10):5431.