Protocol Title:	A Randomised, Double Blind, Three Arm, Single Dose, Parallel Study to Compare the Pharmacokinetics, Pharmacodynamics, Safety, and Immunogenicity Profile of MB09 (Proposed Denosumab Biosimilar) and EU/US sourced Xgeva® in Healthy Male Volunteers
NCT Number:	NCT05299073
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CLINICAL STUDY PROTOCOL
2021-003290-54

A RANDOMISED, DOUBLE-BLIND, THREE-ARM, SINGLE-DOSE, PARALLEL STUDY TO COMPARE THE PHARMACOKINETICS, PHARMACODYNAMICS, SAFETY, AND IMMUNOGENICITY PROFILE OF MB09 (PROPOSED DENOSUMAB BIOSIMILAR) AND EU/US-SOURCED XGEVA® IN HEALTHY MALE VOLUNTEERS

MB09-A-01-19

Sponsor:	mAbxience Research S.L. [redacted].
Sponsor Contact:	[redacted] Clinical Project Manager [redacted]
Medical Monitor:	[redacted] Medical Advisor [redacted]
Version of Protocol:	2.0
Date of Protocol:	[redacted]

CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation Guideline E6(R2): Good Clinical Practice.

SIGNATURE PAGE

PROTOCOL TITLE: A Randomised, Double-Blind, Three-Arm, Single-Dose, Parallel Study to Compare the Pharmacokinetics, Pharmacodynamics, Safety, and Immunogenicity Profile of MB09 (Proposed Denosumab Biosimilar) and EU/US-sourced Xgeva® in Healthy Male Volunteers

PROTOCOL NUMBER: MB09-A-01-19

[redacted]
Medical Advisor

Date

[redacted]
Clinical Project Manager

Date

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree to conduct the study as outlined in the protocol titled "A Randomised, Double-Blind, Three-Arm, Single-Dose, Parallel Study to Compare the Pharmacokinetics, Pharmacodynamics, Safety, and Immunogenicity Profile of MB09 (Proposed Denosumab Biosimilar) and EU/US-sourced Xgeva® in Healthy Male Volunteers" in accordance with the guidelines and all applicable government regulations. I have read and understand all sections of the protocol.

Signature of Principal Investigator	Date

Printed Name of Principal Investigator

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1. INTRODUCTION

1.1 BACKGROUND

Denosumab, the active substance of Xgeva® manufactured and marketed by Amgen in the EU and US, is a human mAb (IgG2) that targets and binds with high affinity and specificity to RANKL. It prevents the RANKL/RANK interaction from occurring, thus resulting in reduced osteoclast numbers and function, thereby decreasing bone resorption and cancer-induced bone destruction.

MB09 is a medicinal product containing mAb denosumab as the active substance, developed by mAbxience as a biosimilar product to Xgeva. In a preliminary assessment, MB09 and Xgeva were proven to be analytically similar in terms of the physicochemical (structure, conformation, post-translational modifications including charge variants and glycosylation profile, and product purity), and biological attributes, using an exhaustive panel of state-of-the-art orthogonal and complementary analytical methods. The objective of developing MB09 is to obtain a biosimilar product to Xgeva in all aspects, ie, not only analytical characteristics evaluated *in vitro*, but also in terms of clinical results.

Further information on the study drugs can be found in the investigator's brochure (mAbxience 2021).

1.2 RATIONALE FOR STUDY

mAbxience is using a similarity-by-design approach for development of the proposed biosimilar, MB09. Following the principles laid out in the current international regulatory guidelines (DHHS 2015a, 2015b, 2019; EMA 2012, 2013, 2014a, 2014b), mAbxience has designed an overall development program to establish similarity between MB09 and Xgeva, tailoring the design of the studies to focus on the molecule's mode of action and analytical similarity between reference medicinal product and MB09. There is no specific target group in the clinical development of a denosumab biosimilar, MB09 as the indications will comprise both males and females. As per the biosimilar development guidelines (DHHS 2016; EMA 2014), it is expected that the safety and efficacy of MB09 would be extrapolated to all indications when such biosimilar comparability to the reference medicinal product is demonstrated by thorough physicochemical and structural analyses as well as by in vitro functional tests, complemented with clinical data (efficacy, safety, and/or PK/PD) in 1 therapeutic indication.

This study planned in healthy male volunteers is part of the clinical development program for MB09 (which will also include a clinical trial in postmenopausal women), and is designed to assess the bioequivalence of MB09 compared with EU- and US-sourced Xgeva.

1.3 RATIONALE FOR DOSE SELECTION

Denosumab displays nonlinear PK due to target-mediated drug elimination at lower doses (>20 mg and <60 mg). However, for doses of 60 mg and above, approximately dose-proportional increases in exposure are seen (linear nontarget-mediated drug disposition). The use of a subtherapeutic dose is considered more sensitive to detect PK differences between MB09 and Xgeva. A lower dose would also limit the exposure and therefore be considered safer for administration in healthy volunteers.

This study is foreseen as part of the clinical development plan to demonstrate PK bioequivalence, and similar PD, immunogenicity and safety profiles of MB09 and Xgeva. When used in the same way as Xgeva, following the same warnings and precautions, it is anticipated that MB09 will provide the same benefits with no difference in risks.

Further information on dose selection, the known and expected benefits and risks, and reasonably anticipated AEs of MB09 may be found in the investigator's brochure (mAbxience 2021).

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objectives of this study are to assess the bioequivalence of single SC doses in healthy subjects of:

- MB09 versus EU-sourced Xgeva
- MB09 versus US-sourced Xgeva
- EU-sourced Xgeva versus US-sourced Xgeva

2.2 SECONDARY OBJECTIVES

The secondary objectives of this study are:

- To evaluate and compare the derived PK and PD of single SC doses of MB09 and EU-sourced Xgeva and MB09 and US-sourced Xgeva in healthy subjects
- To evaluate the safety, tolerability, and immunogenicity of single SC doses of MB09, EU-sourced Xgeva, and US-sourced Xgeva in healthy subjects

3. STUDY DESIGN

This is a Phase 1, double-blind, randomised, single-dose, bioequivalence study to compare the PK, PD, safety, and immunogenicity of MB09 and EU/US-sourced Xgeva in 3 parallel arms.

Healthy male volunteers who meet all inclusion and none of the exclusion criteria will be randomly assigned to receive either 35 mg of MB09 SC (Study Arm 1) or 35 mg of EU-sourced Xgeva SC (Study Arm 2) or 35 mg of US-sourced Xgeva SC (Study Arm 3) in 1:1:1 ratio. The subjects will be stratified based on their body weight.

The study will consist of a screening period (Days -30 to -2), check-in (Day -1), treatment period (Day 1), follow-up period (Days 2 to 252) and an EOS visit (Day 253).

The PK, PD, safety, and immunogenicity endpoints will be evaluated in this study.

Subjects will be confined to the clinical unit from Day -1 until discharge on Day 2. The duration of the study, excluding screening, is approximately 36 weeks.

3.1 SCHEDULE OF EVENTS

	Screening	Check-in	Treatment				Follow-up																		EOS
Day	-30 to -2	-1	1				2	3	4	6	8	11	15	22	29	43	57	71	85	99	113	141	169	197	225	253
Procedure[a] Time Postdose	—	—	Pre dose	H0	H8	H16	H24	H48	H72						M1	M1.5	M2	M2.5	M3	M3.5	M4	M5	M6	M7	M8	M9
Admission to clinic		X																								
Discharge from clinic[b]							X																			
Outpatient visit[c]	X							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Informed consent	X																									
Demographics	X																									
Serology[d]	X																									
Inclusion/exclusion criteria	X	X																								
Medical history	X	X																								
Urine drug screen/alcohol test[e]	X	X																								
Height, weight, and BMI[f]	X	X																								X
Physical examination[g]	X	X																							X	X
Dental and otolaryngological examination[h]	X																									
Vital sign measurements[i]	X	X	X		X		X			X				X				X				X			X	X
12-lead ECG[j]	X	X	X		X		X			X																X
Clinical laboratory testing[k]	X	X					X			X				X		X		X		X		X			X	X
COVID-19 test[l]	X																									
Randomisation[m]		X																								
Study drug administration[n]				X																						
PK sample collection[o]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PD sample collection[o]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity sample collection[p]			X									X				X				X			X		X	X
AEs[q]	◄ X ►																									
Prior/concomitant medications	◄ X ►																									

Abbreviations: AEs, adverse events; BMI, body mass index; COVID-19, coronavirus disease 2019; ECG, electrocardiogram; EOS, end of study; H, hour; ICF, informed consent form; M, month, PD, pharmacodynamic; PK, pharmacokinetic; QTcF, QT interval corrected for heart rate using Fridericia's formula; SC, subcutaneous.

Notes:

[a] When procedures overlap or occur at the same time point, all blood draws should follow vital signs or ECGs, and PK sampling should be timed to occur last and as close to the scheduled time point as possible.

[b] Discharge following 24-hour PK/PD sample collection.

[c] Follow-up visits will occur from Day 3 through EOS visit on Day 253.

[d] Serology testing will include hepatitis B surface antigen, anti-hepatitis B core antigen, anti-hepatitis B surface antigen, hepatitis C virus antibodies, and human immunodeficiency virus types 1 and 2 antibodies. Hepatitis B DNA test can be done as a confirmatory test in exceptional cases, if needed.

[e] Urine drug screen/alcohol test (urine/breath) will occur at screening and check-in per the clinic's standard procedures.

[f] The BMI (kg/m^2) will be calculated at check-in using the following formula: weight (kg)/height (m^2). Height will be measured at screening only. Only weight will be measured at EOS visit.

(g) A full physical examination will be performed at screening (at minimum, assessment of skin, head, oral cavity, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities). A brief physical examination will be performed at check-in, Day 225, and EOS (at minimum, assessment of oral cavity, skin, lungs, cardiovascular system, and abdomen [liver and spleen]). Interim physical examinations may be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

(h) To be performed by dentist and otolaryngologist, respectively at screening only.

(i) Vital signs will include systolic and diastolic blood pressure, respiratory rate, pulse rate, and tympanic temperature and will be measured after the subject has been in the supine position for at least 5 minutes. Tympanic temperature will be measured at screening, Days 2, 22, 225, and EOS. Vital signs will be measured within 15 minutes prior to study drug dosing on Day 1.

(j) Single 12-lead ECG recordings will be made after the subject has been in the supine position for at least 5 minutes. A single repeat measurement is permitted at screening for eligibility determination. Measurements of the following intervals will be reported: RR interval, PR interval, QRS width, QT interval, and QTcF. Assessments should include comments on whether the tracings are normal or abnormal; rhythm; presence of arrhythmia or conduction defects; morphology; any evidence of myocardial infarction; or ST-segment, T-wave, and U-wave abnormalities.

(k) A complete list of assessments is provided in Section 6.4.2. Blood and urine samples will be collected after overnight fasting for 10 hours and prepared per the clinic's standard procedures. The same visit windows will apply for safety laboratory sample collection as for PK (refer to footnote (o)).

(l) The clinic will follow standard procedures and/or local guidelines with respect to COVID-19 testing at screening and any other timepoints during the study, if deemed necessary by the investigator.

(m) Randomisation should be done on Day -1 or Day 1 prior to initiating any study procedures.

(n) The time of study drug dosing will be called "0" hour and is denoted with grey shading. A single SC dose of 35 mg of the study drug will be administered in the upper arm to each subject. Subjects will remain semi-supine for the first 4 hours after administration unless moving is medically necessary, requires procedures, or means going to the washroom.

(o) Blood samples for PK analysis of the study drug (MB09 or Xgeva) in plasma and PD analysis of area under the effect curve will be collected up to 2 hours prior to study drug dosing and after dosing at 8 and 16 hours (± 2 hours), 24, 48, and 72 hours (± 4 hours), Days 6, 8, and 11 (± 1 day), Days 15, 22, and 29 (± 2 days), Days 43, 57, 71, 85, 99, 113, 141, 169, 197, 225, and 253 (± 3 days). At each time point, blood samples will be collected after overnight fasting of at least 10 hours.

(p) Samples for immunogenicity analysis will be obtained prior to study drug dosing and at the timepoints indicated in the schedule of events. If hypersensitivity occurs after the study drug dosing, additional samples for immunogenicity testing may be obtained at the discretion of the investigator to determine serum sickness.

(q) Adverse events and SAEs will be assessed from the time of signing the ICF until EOS and should be followed until they are resolved, stable, or judged by the investigator to be not clinically significant.

4. STUDY POPULATION

Adequate number of healthy male subjects will be screened and enrolled at selected centres in Poland to have 204 evaluable subjects.

4.1 INCLUSION CRITERIA

Each subject must meet all of the following criteria to be enrolled in this study:

1. The subject is a male of any race, between 28 and 55 years of age, inclusive, at screening.

2. The subject has a BMI between 18.5 and 29.9 kg/m^2, inclusive, (total body weight between 60 and 95 kg, inclusive) at screening and check-in.

3. The subject is considered by the investigator to be in good general health as determined by medical history, clinical laboratory test results (congenital nonhaemolytic hyperbilirubinemia [eg, Gilbert's syndrome] is acceptable), vital sign measurements (systolic BP ≥90 mm Hg and ≤140 mm Hg, diastolic BP ≥50 mm Hg and ≤90 mm Hg), 12-lead ECG results, and physical examination findings at screening and check-in.

4. The subject must use an adequate method of contraception (eg, condom) or be willing to practice sexual abstinence during the study starting from the day of dosing and for 140 days after dosing. The subject must agree to not donating sperm during the study and for at least 140 days after dosing. Participating subject's female partner of childbearing potential should use an additional form of contraception such as an intra-uterine device, barrier method with spermicide, oral contraceptive, injectable progesterone, or sub-dermal implant starting from the male partner's day of dosing until at least 140 days after dosing. The female partner of the participating subject should be familiar with the use of the respective contraceptive methods. Intra-uterine devices and hormonal methods for contraception should be used for at least 1 menstruation cycle prior to the administration of study drug.

5. The subject must be able to comprehend and willing to sign an ICF and to abide by the study restrictions. Subjects must have signed an ICF before any study-related procedure or evaluation is performed.

4.2 EXCLUSION CRITERIA

Subjects meeting any of the following criteria will be excluded from the study:

1. The subject has had previous exposure to denosumab.

2. The subject has a significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, haematological, cardiovascular, gastrointestinal, neurological, respiratory, endocrine, or psychiatric disorder, as determined by the investigator.

3. The subject has a history of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the investigator.

4. The subject has any current or recent history of infections, including localised infections (within 2 months prior to screening for any serious infection that requires hospitalisation or IV anti-infective or within 14 days prior to screening for any active infection which requires oral treatment).

5. The subject has a dental or jaw disease requiring oral surgery or dental surgery within 6 months prior to study product administration or plans to have dental surgery within 6 months after dosing.

6. The subject has a history of osteomyelitis or osteonecrosis of the jaw requiring suturing within 30 days before dosing, or within 30 days after the last study visit.

7. The subject has a medically significant dental disease or dental neglect, with signs and/or symptoms of local or systemic infection that would likely require a dental procedure during the course of the study. Standard dentistry treatments (eg, dental filling or prophylaxis/cleaning) are allowed.

8. The subject has clinically relevant history of alcoholism, addiction or drug/chemical abuse prior to check-in, and/or positive urinary test for alcohol or drugs of abuse at screening or check-in.

9. The subject has positive hepatitis panel (HBV and HCV) or positive HIV test. Subjects whose results are compatible with prior immunisation and not infection may be included at the discretion of the investigator.

10. The subject has participated in a clinical study involving administration of an investigational drug (new chemical entity), with dosing in the past 90 days prior to Day -1, or within 5 half-lives of the investigational drug used in the study, whichever is longer.

11. The subject has used or intends to use slow-release medications/products considered to still be active within 30 days prior to check-in, unless deemed acceptable by the investigator.

12. The subject has used or intends to use any nonprescription medications/products (except paracetamol [up to 2 g/day] and ibuprofen [800 mg/day]), including vitamins, minerals, supplements (eg, Biotin), and phytotherapeutic/herbal/plant-derived preparations within 7 days prior to check-in, unless deemed acceptable by the investigator. Vitamin C, vitamin D, and calcium in daily recommended doses (≤1000 mg elemental calcium and 1000 IU vitamin D based on screening levels of vitamin D) are allowed.

13. The subject has received the COVID-19 vaccine within 14 days before Day 1 or plans to receive a COVID-19 vaccine within 12 weeks after study drug dosing or has positive test for COVID-19 during screening or presence of COVID-19 symptoms within 4 weeks prior to Day -1.

14. The subject has received a live or attenuated vaccine within 3 months prior to screening or has the intention to receive a vaccine during the study. The subject intends to travel to a region where a vaccination will be required due to endemic disease during the study.

15. The subject has used tobacco- or nicotine-containing products within 1 year prior to check-in or anytime during the study, or has a positive cotinine test upon screening or check-in.

16. The subject has donated blood within 60 days prior to dosing, plasma from 14 days prior to screening, or platelets from 42 days prior to dosing.

17. The subject has poor peripheral venous access.

18. Subjects who, in the opinion of the investigator, should not participate in this study.

4.3 WITHDRAWAL CRITERIA

General criteria for subject withdrawal and the handling of withdrawals can be found in Appendix 2.

4.4 SUBJECT REPLACEMENT

At the discretion of the investigator, and after consultation with the medical monitor any subject who is withdrawn or discontinued from the study for reasons other than those related to study treatment may be replaced to retain the target of 204 evaluable subjects (68 subjects in each study arm). Any replacement subject will be assigned to receive the same treatment as the subject he is replacing.

5. STUDY TREATMENTS

5.1 TREATMENTS ADMINISTERED

All subjects will receive the study treatments as described in Section 3 and according to the SOE (Section 3.1). Additional instructions for dosing can be found in the SOE.

5.2 INVESTIGATIONAL PRODUCTS

The study drugs that will be used are as follows:

Product	Supplied Formulation
MB09 (Study Arm 1, test)	Vial containing 70 mg/mL
EU-sourced Xgeva® (Study Arm 2, reference)	Vial containing 70 mg/mL
US-sourced Xgeva® (Study Arm 3, reference)	Vial containing 70 mg/mL

Each of the investigational products contains the following inactive excipients: glacial acetic acid, sodium hydroxide (for pH adjustment - acetate buffer is formed by mixing acetic acid with sodium hydroxide), sorbitol (E420), polysorbate 20, and water for injection.

Further information on the study drugs can be found in the MB09 investigator's brochure (mAbxience 2021), EU-sourced Xgeva summary of product characteristics (Amgen 2020), and US-sourced Xgeva prescribing information (Amgen 2020).

5.2.1 Study Drug Preparation and Storage

The sponsor will provide the investigators and clinical units with adequate quantities of MB09, EU-sourced Xgeva, and US-sourced Xgeva vials. Unblinded clinical unit pharmacists will prepare the study treatments. A single 35 mg SC dose of the randomly assigned study drug will be administered in the upper arm by the blinded clinical unit personnel to each subject at the clinical unit according to the SOE (Section 3.1).

All study drugs must be stored refrigerated between 2ºC and 8ºC according to the labeled instructions in a secure cabinet or room with access restricted to necessary clinic personnel. The sites will be required to keep a temperature log to establish a record of compliance with storage conditions. Refer to the pharmacy manual for further instructions on storage, preparation, and administration of the study drugs.

5.2.2 Study Drug Accountability

The unblinded clinical unit pharmacists will maintain an inventory of the supplies, ensuring that the study drugs are received intact and in appropriate amounts, before completing the supplies receipt. The investigators will maintain accurate records of receipt of all study drugs, including dates of receipt. Accurate records will be kept at all times regarding when and how much study drug is dispensed and used by each subject in the study. Reasons for departure from the expected dispensing regimen must be communicated to the sponsor and recorded. The unblinded clinical monitor will be responsible to verify that the study drugs receipt records are correctly maintained by the sites. The unblinded clinical monitor may also check the study drug supplies inventory and records at any time during the study. At the completion of the study, and to satisfy regulatory requirements regarding drug accountability, all study drugs will be reconciled and retained or destroyed according to applicable regulations post approval from the sponsor.

5.3 METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUPS

PPD will generate the randomisation schedule. Subjects who meet all inclusion and none of the exclusion criteria will be randomly assigned to 1 of the 3 study arms. Randomisation numbers (in sequential order) will be assigned before the study drug is administered on Day 1. Randomisation will be stratified based on the subject's body weight: 60 to <80 kg and 80 to 95 kg.

5.4 BLINDING

5.4.1 Blinding Procedures

This study will employ a double-blind study design. MB09 and Xgeva will be packed in identical boxes. The unblinded pharmacists will be responsible for preparing and dispensing the study drug in a manner consistent with maintaining the blind.

5.4.2 Breaking the Blind

The sites will be responsible for maintaining the blind throughout the study. If a subject becomes seriously ill during the study, the blind will be broken upon the investigator's approval only if knowledge of the administered study drug will affect that subject's available treatment options. In the event of a medical emergency requiring identification of the study drug administered to an individual subject, the investigator will make every attempt to contact the medical monitor to explain the need for opening the code within 24 hours of opening the code. The mAbxience pharmacovigilance department will have access to the randomisation code, if SUSARs, which are subject to expedited reporting, will be unblinded before submission to the regulatory authorities. The unblinded personnel will be predefined and documented before breaking the study blind. The investigator will be responsible for documenting the time, date, reason for the code break, and the names of the personnel involved. Subjects who are unblinded can continue in the study at the investigator's discretion.

The study will remain blinded to the investigators, subjects, and predefined mAbxience and PPD blinded personnel until all subjects have completed the study and the database has been finalised for study closure.

6. STUDY PROCEDURES

Before performing any study procedures, all potential subjects will sign an ICF as outlined in Section 9.4.2.3.

- Details of additional standard study procedures can be found in Appendix 2.
- The total amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.

6.1 PHARMACOKINETIC ASSESSMENTS AND ENDPOINTS

The following denosumab PK parameters will be calculated as MB09 and Xgeva endpoints using standard noncompartmental methods:

Primary endpoints: $AUC_{0\text{-last}}$ and C_{max}

Secondary endpoints: $AUC_{0\text{-}\infty}$, T_{max}, CL, $t_{1/2}$

- The timing and frequency of PK sample collection is listed in the SOE (Section 3.1).
- Definitions of the PK parameters can be found in the list of abbreviations, Appendix 1.

6.1.1 Pharmacokinetic Sample Collection

Details for the collection, processing, storage, and shipping of PK samples will be provided to the clinical units separately in a laboratory manual.

6.1.2 Pharmacokinetic Sample Analysis

Pharmacokinetic samples will be analyzed using a validated MSD-ECL assay for denosumab in human plasma. Assay results and validation details will be provided in a separate bioanalytical report.

6.2 PHARMACODYNAMIC ASSESSMENTS AND ENDPOINTS

The following plasma serum C-terminal telopeptide of Type 1 collagen (sCTX) parameter will be calculated as PD endpoint for determination of proposed bioequivalence between test and reference products:

Secondary endpoint: $AUEC_{0\text{-last}}$.

- The timing and frequency of PD sample collection is listed in the SOE (Section 3.1).
- Definitions of the PD parameter can be found in the list of abbreviations, Appendix 1.

6.2.1 Pharmacodynamic Sample Collection

Details for the collection, processing, storage, and shipping of PD samples will be provided to the clinical units separately in a laboratory manual.

6.2.2 Pharmacodynamic Sample Analysis

Pharmacodynamic samples will be analyzed for sCTX using validated ELISA. Assay results and validation details will be provided in a separate bioanalytical report.

6.3 IMMUNOGENICITY ASSESSMENTS AND ENDPOINTS

Denosumab ADA and neutralizing antibodies will be assessed by a validated MSD-ELC assay.

- The timing and frequency of immunogenicity sample collection is listed in the SOE (Section 3.1).
- Definitions of the immunogenicity parameters can be found in the list of abbreviations, Appendix 1.

6.3.1 Immunogenicity Sample Collection

Details for the collection, processing, storage, and shipping of immunogenicity samples will be provided to the clinical units separately in a laboratory manual.

6.3.2 Immunogenicity Sample Analysis

The analysis will involve both a screening, confirmatory, and titre assay to confirm positive results. Immunogenicity samples will be analyzed for anti-MB09 and neutralizing anti-MB09 antibodies using validated MSD-ECL assay. Assay results and validation details will be provided in a separate bioanalytical report.

6.4 SAFETY ASSESSMENTS AND ENDPOINTS

The timing and frequency of all safety assessments is listed in the SOE (Section 3.1).

Safety and tolerability endpoints will include monitoring and recording of AEs, clinical laboratory test results (haematology, coagulation, serum chemistry, and urinalysis), vital sign measurements, 12-lead ECG results, and targeted physical examination findings.

For all safety assessments, the investigator will determine whether results are clinically significant, which is defined as any variation in a result that has medical relevance and may result in an alteration in medical care (eg, active observation, diagnostic measures, or therapeutic measures). If clinical significance is noted, the result and reason for significance will be documented in the subject's source document and an AE reported on the AE page of

the subject's eCRF. The investigator will monitor the subject even after EOS, if need be, until the result has reached the reference range or the result at screening, or until the investigator determines that follow-up is no longer medically necessary. Refer Section 9.3 for details on AE definitions and reporting.

6.4.1 Adverse Events

Definitions and procedures for reporting of AEs can be found in Appendix 3. For this study, the following contact information is to be used for SAE reporting:

mAbxience Pharmacovigilance:	Telephone (24 hour): 0034-689-838-874 Fax: 0034-917-711-590 Email: pharmacovigilance@mabxience.com

6.4.2 Clinical Laboratory Assessments

The following clinical laboratory assessments will be performed:

Haematology	Leukocyte count and percentage and absolute differentials (basophils, eosinophils, lymphocytes, monocytes, neutrophils), haematocrit, haemoglobin, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, mean corpuscular volume, platelet count, red blood cell count, and red blood cell distribution width
Coagulation	INR, PT, aPTT
Serum Chemistry	ALT, albumin, ALP, AST, bilirubin (total, direct, indirect), BUN, calcium, chloride, cholesterol (total, high-density lipoprotein, and calculated low-density lipoprotein), creatine kinase, gamma-glutamyltransferase, globulin, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total protein, triglycerides, uric acid, vitamin D, creatinine, and GFR GFR will be calculated by the MDRD equation: $175 \times (\text{standardized serum creatinine}/88.4)^{-1.154} \times (\text{age})^{-0.203} \times (1.212 \text{ if black})$
Urinalysis	Appearance, bilirubin, colour, glucose, ketones, leukocyte esterase, reflex microscopy (performed if protein or blood/erythrocytes are detected and reported as abnormal on dipstick; and includes bacteria, casts, crystals, epithelial cells, red blood cells, and white blood cells), nitrites, occult blood, pH, protein, specific gravity, turbidity, and urobilinogen
Serology	Hepatitis B surface antigen, anti-hepatitis B core antigen, anti-hepatitis B surface antigen, hepatitis B DNA test (optional), HCV antibody, and HIV antibody types 1 and 2 (screening only)

Other analyses	All subjects: COVID-19 test, alcohol test (urine/breath), urine drug screen (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, cotinine, methamphetamines, tricyclic antidepressants, and opiates)

- The clinical laboratory that performs the tests will provide the reference ranges for all clinical laboratory parameters.

- Clinical laboratory tests should not be repeated unless deemed necessary by the investigator; re-evaluation may be allowed once for assessment of inclusion and exclusion criteria or evaluation of clinical laboratory abnormalities.

7. STATISTICAL ANALYSIS PLANS

7.1 SAMPLE SIZE CALCULATIONS

The sample size for this study is based on a statistical power calculation. A CV value of 33% was estimated for AUC parameter (which showed the highest variability) based on previous PK studies conducted at a dose of 60 mg or 1 mg/kg. Assuming a ratio of AUC and C_{max} between 0.95 and 1.05, 68 PK-evaluable subjects per arm would be required to provide at least 90% power to conclude bioequivalence of MB09 and Xgeva. Thus, 204 evaluable subjects will be required in all.

Assuming a 20% dropout rate, approximately 255 subjects are planned to be enrolled in this study. Enrollment could be stopped when the target of having 204 evaluable subjects is achieved. Subjects will be randomly assigned to 1 of 3 study arms in a 1:1:1 ratio.

7.2 ANALYSIS SETS

The analysis populations are as follows:

- The PK population will include subjects who receive the study drug, who do not have major protocol deviations, and have sufficient data to calculate primary PK endpoints.

- The safety population will include all subjects who receive the study drug.

7.3 STATISTICAL ANALYSES

Details of all statistical analyses will be described in a separate statistical analysis plan. All data collected will be presented in data listings. Data from subjects excluded from an analysis

population will be presented in the data listings, but not included in the calculation of summary statistics.

For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarised using descriptive statistics (number of subjects, mean, median, SD, minimum, and maximum).

Baseline demographic and background variables will be summarised overall for all subjects. The number of subjects who enroll in the study and the number and percentage of subjects who complete the study will be presented. Frequency and percentage of subjects who withdraw or discontinue from the study and the reason for withdrawal or discontinuation will also be summarised.

7.3.1 Pharmacokinetic Analyses

Individual plasma concentration and time deviation data will be presented in a data listing. Plasma concentration data will be summarised by time point for each treatment using the following descriptive statistics: number of subjects, arithmetic mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum. Individual and mean plasma concentration versus scheduled time profiles will be presented in figures on both linear and semilogarithmic scales.

The PK parameters of MB09 and Xgeva will be analyzed based on the actual sampling times. All parameters will be calculated using the latest version of Phoenix® WinNonlin® (Certara USA Inc., Princeton, New Jersey) or SAS® (SAS Institute Inc., Cary, North Carolina). The individual PK parameters will be presented in data listings and summarised by treatment using the following descriptive statistics: number of subjects, mean, SD, CV, median, minimum, and maximum. Geometric means will be included for C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}\infty}$.

An ANOVA model with fixed effects for treatment will be performed on the natural log-transformed values of C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}\infty}$ to assess the relative bioequivalence of the test drug (MB09) to the reference drugs (EU/US-sourced Xgeva), as well as for comparing EU-sourced Xgeva to US-sourced Xgeva. The geometric least squares means and corresponding 90% CIs will be computed for C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}\infty}$ by taking the antilog of the least squares means from the linear mixed-effect model on the natural logarithms of the corresponding PK parameters. A 90% CI for the ratio will be constructed as the antilog of the confidence limits of the mean difference. No adjustment will be made for multiplicity.

Bioequivalence will be concluded if the 90% CIs for the test to reference ratios of the geometric least square means for $AUC_{0\text{-last}}$ and C_{max} are entirely contained within the [80%, 125%] interval.

Nonparametric methods will be used to examine difference in medians of T_{max} for MB09 and Xgeva.

7.3.2 Pharmacodynamic Analyses

Individual observed concentrations of sCTX and time deviation data will be presented in a data listing. Observed concentrations of sCTX will be summarised by time point for each treatment using the following descriptive statistics: number of subjects, arithmetic mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum. Individual and mean observed concentrations of sCTX versus scheduled time profiles will be presented in figures on linear scales.

The PD parameters of MB09 and Xgeva will be analyzed based on the actual sampling times. All parameters will be calculated using the latest version of Phoenix® WinNonlin® (Certara USA Inc., Princeton, New Jersey) or SAS® (SAS Institute Inc., Cary, North Carolina) without baseline adjustment. The individual PD parameters for sCTX will be presented in data listings and summarised by treatment using the following descriptive statistics: number of subjects, mean, SD, CV, median, minimum, and maximum. Geometric means will be included for $AUEC_{0\text{-last}}$.

An ANOVA model with fixed effects for treatment will be performed on the natural log-transformed values of area under the effect versus time curve (AUEC) to compare between the test drug (MB09) to the reference drugs (EU/US-sourced Xgeva). The geometric least squares means and corresponding 90% CIs will be computed for AUEC by taking the antilog of the least squares means from the linear mixed-effect model on the natural logarithms of the corresponding PD parameters. A 90% CI for the ratio will be constructed as the antilog of the confidence limits of the mean difference. No adjustment will be made for multiplicity.

Bioequivalence in PD biomarker will be reported as the test to reference ratio of geometric means and its corresponding 90% CI for AUEC PD parameter.

7.3.3 Safety and Immunogenicity Analyses

Adverse events will be coded by preferred term and system organ class using MedDRA Version 24. All AE data will be presented in a data listing. Treatment-emergent AEs will be

summarised by treatment and overall, as well as by severity and relationship to study drug. Serious AEs and AEs leading to discontinuation of study drug will also be presented in the data listings and summarised by treatment and overall.

Actual values and changes from baseline for clinical laboratory test results, vital sign measurements, and 12-lead ECG results will be summarised by treatment at each time point using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Shift tables will be generated for clinical laboratory test results. Physical examination findings will be presented in a data listing.

The incidence of ADA to denosumab and the neutralizing potential and titre of positive ADAs will be reported. All immunogenicity data will be presented in the data listings.

7.4 HANDLING OF MISSING DATA

Plasma denosumab concentrations that are below limit of quantification (BLQ) will be treated as zero for descriptive statistics; mean BLQ concentrations will be presented as BLQ, and the SD and CV will be reported as not applicable. Missing concentrations will be excluded from the calculation of concentration summary statistics.

For the PK analysis, denosumab BLQ values will be treated as zero with the exception that a BLQ value between 2 quantifiable concentrations will be set as missing. Missing concentrations will be treated as missing from the PK parameter calculations. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal phase, those concentrations after BLQ concentrations will be treated as missing.

For the PD analysis, sCTX concentrations that are BLQ will be treated as zero for descriptive statistics; mean BLQ concentrations will be presented as BLQ, and the SD and CV will be reported as not applicable. Missing sCTX concentrations will be excluded from the calculation of concentration summary statistics.

For the PD analysis, all sCTX BLQ values will be treated as one-half the lower limit of quantification for the estimation of PD parameters, and missing sCTX concentrations will be treated as missing.

7.5 INTERIM ANALYSES

No formal interim analyses will be performed in this study.

8. REFERENCE LIST

[redacted]

9. APPENDICES

9.1 APPENDIX 1: LIST OF ABBREVIATIONS

Abbreviation	Term
ADA	anti-drug antibodies
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
$AUC_{0\text{-last}}$	area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration
$AUC_{0\text{-}\infty}$	area under the plasma concentration versus time curve from time 0 extrapolated to infinity
AUEC	area under the effect versus time curve
$AUEC_{0\text{-last}}$	area under the effect versus time curve from time 0 to the last quantifiable concentration
BLQ	below limit of quantification
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
C_{max}	maximum observed plasma concentration
COVID-19	coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EOS	end of study
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee

Abbreviation	Term
IgG	immunoglobulin G
INR	international normalised ratio
IV	intravenous
mAb	monoclonal antibody
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MSD-ELC	Meso Scale Discovery-electrochemiluminescence
NCI	National Cancer Institute
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PT	prothrombin time
RANK	Receptor Activator of Nuclear Factor Kappa-B (NFκB)
RANKL	Receptor Activator of Nuclear Factor Kappa-B (NFκB) Ligand
SAE	serious adverse event
SC	subcutaneous(ly)
SD	standard deviation
sCTX	serum C-terminal telopeptide of Type 1 collagen
SOE	schedule of events
SUSAR	suspected unexpected serious adverse reaction
T_{max}	time to reach maximum observed serum concentration
$t_{1/2}$	terminal half-life
USA	United States of America

9.2 APPENDIX 2: STANDARD PROCEDURES

9.2.1 Removal of Subjects From Therapy or Assessment

9.2.1.1 General Criteria for Withdrawal

Subjects can withdraw consent and discontinue from the study at any time including prior to study drug administration, for any reason, without prejudice to further treatment.

The investigator may withdraw a subject from the study if the subject meets any of the following criteria:

1. Protocol deviation of concern occurs (eg, protocol deviations that may affect study objectives, or it is discovered that the subject has entered the study in violation of the protocol)

2. Experiences an SAE or intolerable AE(s) that, in the investigator's opinion, requires withdrawal from the study

3. Requests early discontinuation for any reason

The investigator can also withdraw subjects if the sponsor terminates the study. If withdrawal is considered because of an SAE or intolerable AE, the investigator will confer with the sponsor. If a subject is discontinued because of an AE, the event will be followed until it is resolved, stable, or judged by the investigator to be not clinically significant. If a subject withdraws prematurely after dosing, he will be asked to return to the clinical unit and will undergo all EOS (ie, Day 253) assessments.

At the discretion of the investigator, and after consultation with the medical monitor, any subject who withdraws for reasons other than those related to study treatment, before completing the study may be replaced to retain the target of 204 evaluable subjects. Any replacement subject will be assigned to receive the same treatment as the subject he is replacing.

9.2.1.2 Handling of Withdrawals

When a subject withdraws from the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the eCRF. Whenever possible, any subject who prematurely withdraws from the study will undergo all EOS assessments. Any subject who fails to return for final assessments will be contacted by the site in a reasonable attempt to have

them comply with the protocol. The status of subjects who fail to complete final assessments will be recorded in the respective subject's source document and transferred into the eCRF.

Eligible subjects who meet all inclusion/exclusion criteria but are unable to participate in the study due to a scheduling conflict may be rescreened. A subject who has failed screening may be rescreened at the discretion of the investigator and sponsor. In these cases, a new screening number must be assigned for each subject who is rescreened, and a new ICF must be signed.

9.2.2 Prior and Concomitant Medications and Therapies and Other Study Restrictions

Subjects should abstain from alcohol, caffeine-, xanthine-containing beverages or food (eg, coffee, tea, chocolate, and caffeinated sodas, colas), grapefruit juice, Seville orange containing products (eg, marmalade), or products containing any of these, from 48 hours prior to study drug dosing and throughout the duration of the study. Subjects should also abstain from strenuous activity/exercise or contact sports within 24 hours before the first dose of study drug and throughout the duration of the study, including 7 days before nonresidential visits, and will otherwise maintain their normal level of physical activity during this time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

Restrictions for prior and concomitant medications and therapies are provided in Sections 4.1 and 4.2. Prior and concomitant medications and therapies will be coded using the latest version of the World Health Organization Drug Dictionary.

Other restrictions as described in the study protocol also apply.

9.2.2.1 Prior Medications

Information regarding prior medications taken by the subject within the 30 days before signing the ICF will be recorded in the subject's source document and transferred into the eCRF.

9.2.2.2 Concomitant Medications

Any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the investigator. If a concomitant medication is taken, except for those specified in the protocol, a joint decision will be made by the investigator and the sponsor to continue or discontinue the subject based on the time the medication was administered, its pharmacology and PK, and whether the use of the medication will compromise the safety of the subject or the interpretation of the data. The investigator is

responsible for ensuring that details regarding the medication are adequately recorded in the eCRF.

9.2.3 Treatment Compliance

All subjects will receive the study drug dose in the clinical unit under direct observation of clinic personnel. Clinic personnel will confirm that the subject has received the entire dose of study drug.

The date and time of study drug dosing will be recorded in the subject's source document and transferred into the appropriate page of the eCRF. If a subject is not administered the study drug dose, the reason will be recorded in the source document and transferred into the appropriate page of the eCRF, and the subject will be withdrawn from the study.

9.3 APPENDIX 3: ADVERSE EVENT DEFINITIONS AND REPORTING

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to the sponsor, regardless of their relationship to study drug or clinical significance. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

9.3.1 Adverse Event Definitions

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Subjects will be instructed to contact the investigator at any time after randomisation if any symptoms develop.

A treatment-emergent AE is defined as any event not present before exposure to study drug or any event already present that worsens in intensity or frequency after exposure.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the study drug caused the AE. For the purposes of investigational new drug safety reporting, “reasonable possibility” means that there is evidence to suggest a causal relationship between the study drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

An adverse reaction is any AE caused by a study drug. Adverse reactions belong to a subset of all suspected adverse reactions and indicate that there are reasons to conclude that the study drug caused the event.

An AE or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator’s brochure or if it occurs with specificity or severity that has not been previously observed with the study drug being tested; or, if an investigator’s brochure is not required or available, the AE or suspected adverse reaction is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator’s brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator’s brochure listed only cerebral vascular accidents. “Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the investigator’s brochure as occurring with a class of drugs or as anticipated

from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

An AE or suspected adverse reaction is considered an SAE/SUSAR if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening AE
- Inpatient hospitalisation (other than that for the study drug administration) or prolongation of existing hospitalisation
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly or birth defect

Hospitalisation is to be considered as an overnight admission, except for the following reasons:

- Hospitalisation for diagnostic investigations (eg, scans, endoscopy, sampling for laboratory tests, bone marrow sampling) that are not related to an AE
- Prolonged hospitalisation for technical, practical, or social reasons, in absence of an AE
- Hospitalisation for a procedure that was planned before study participation (ie, before registration or randomisation). This should be recorded in the source documents. Prolonged hospitalisation due to a complication of such procedures remains a reportable SAE.
- Hospitalisation for ≤24 hours in an emergency room

Other events subject to immediate notification (within 24 hours), include but are not limited to:

- Pregnancy of partner study subject or breastfeeding cases via a pregnancy report form
- Medication errors, namely overdose, leading to a suspected adverse reaction

Important medical events that may not result in death, be life threatening, or require hospitalisation may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent

one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalisation, or the development of drug dependency or drug abuse.

An AE or suspected adverse reaction is considered "life threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that might have caused death if it had been more severe.

9.3.2 Eliciting and Documenting Adverse Events

Subjects will be asked a standard question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalised, had any accidents, or used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

In addition to subject observations, AEs will be documented from any data collected on the AE page of the eCRF (eg, laboratory values, physical examination findings, and ECG changes) or other documents that are relevant to subject safety.

9.3.3 Reporting Adverse Events

All AEs and SAEs (including partner pregnancy after study drug dosing) will be assessed from the time of signing the ICF until EOS. Any AE or SAE reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes drug treatment, type of event, time of onset, dosage, investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, any required treatment or evaluations, and outcome. Any AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. A paper partner pregnancy form will be used to inform the sponsor in case the subject's partner becomes pregnant anytime during the study. The form to be used and completion instructions will be provided to the clinical units separately. The subject's partner should read and sign the partner pregnancy ICF, prior to collecting any pregnancy related information. The partner may or may not agree to share all medical records for follow-up. All AEs will be followed until they are resolved, stable, or judged by the investigator to be not clinically significant. The MedDRA Version 24 – 01 March 2021 will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

Any AE that is considered serious by the investigator or which meets SAE criteria (Section 9.3.1) must be reported to the sponsor immediately (within 24 hours after the investigator has confirmed the occurrence of the SAE). The investigator will assess whether there is a reasonable possibility that the study drug caused the SAE. The sponsor will be responsible for notifying the relevant regulatory authorities of any SAE.

Contact information to be used for SAE reporting can be found in Section 6.4.

9.3.4 Assessment of Severity

All AEs will be graded for intensity according to the CTCAE, Version 5.0 – November 2017 (DHHS 2017).

All other laboratory and clinical AEs not outlined in the CTCAE that occur in a subject will be assessed (graded) for intensity and then classified into 1 of 5 clearly defined categories as follows:

- Grade 1 (Mild): Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 (Moderate): Minimal, local, or noninvasive intervention indicated; limits age-appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).
- Grade 3 (Severe): Medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limits self-care activities of daily living (eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4 (Life-threatening): Urgent intervention indicated.
- Grade 5 (Death).

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. An AE characterized as intermittent requires documentation of onset and duration of each episode.

9.3.5 Assessment of Causality

The investigator's assessment of an AE's relationship to study drug is part of the documentation process but is not a factor in determining what is or is not reported in the study.

The investigator will assess causality (ie, whether there is a reasonable possibility that the study drug caused the event) for all AEs and SAEs. The relationship will be classified as follows:

- Not related: There is not a reasonable possibility of relationship to study drug. The AE does not follow a reasonable temporal sequence from study drug administration or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications). This category will include AEs unrelated to the study drugs.

- Related: There is a reasonable possibility of relationship to study drug. The AE follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, or concomitant medications), represents a known reaction to the study drug or other drugs in its class, is consistent with the known pharmacological properties of the study drug, and/or resolves with discontinuation of the study drug (and/or recurs with re-challenge, if applicable). This category will include AEs that may be definitely, probably, or possibly related to the study drugs.

9.3.6 Follow-up of Adverse Events

All AEs must be reported in detail in the subject's source document and transferred into the appropriate page of the eCRF and followed until they are resolved, stable, or judged by the investigator to be not clinically significant.

9.3.7 Reporting Serious Adverse Events

Prompt notification of SAEs by the investigator to the sponsor is essential so that the sponsor can meet its regulatory reporting obligations for the study. If the investigator does not have all of the details regarding the SAE, he/she will not wait until this information becomes available before making the initial report to the sponsor. Contact details are in Table 9-1.

Notification should be made in a detailed written SAE form report within 24 hours of the investigator becoming aware of the event.

All reports should be directed to the pharmacovigilance mailbox. The investigator at the site is responsible for ensuring that a member of the sponsor study team is made aware of any SAE reports that have been transmitted.

Table 9-1 - Contact Details for Reporting SAEs

Contact	Details
Pharmacovigilance reporting email	[redacted]
Pharmacovigilance fax number reporting	[redacted]
SAE reporting email	[redacted]

The paper SAE form, AE record and relevant concomitant medication records should be faxed/emailed to the sponsor within 24 hours of the investigator or any site personnel's knowledge of an SAE. An updated SAE report form should be forwarded to the sponsor within 24 hours of receipt of the new/updated information as relevant. The SAE report form to be used and completion instructions will be provided to the clinical units separately.

Information relating to the subject's subsequent medical progress must be submitted to the sponsor as available, until the SAE has subsided or, in the case of permanent impairment, until it stabilises, and the overall clinical outcome has been ascertained.

The investigator will also provide additional information, including a copy of the following documents (where applicable):

- Copies of test results, as available
- Hospital discharge summary
- Autopsy report

9.3.8 Reporting of Suspected Unexpected Serious Adverse Reactions

All SUSARs will be subjected to expedited reporting. The sponsor and/or PPD shall ensure that all relevant information about a SUSAR that is fatal or life-threatening is reported to the relevant competent authorities and IEC within 7 days after knowledge by the sponsor of such

a case and that relevant follow up information is communicated within additional 8 days. All other SUSARs will be reported to the relevant competent authorities and IEC within 15 days after knowledge by the sponsor of such a case.

All investigators should follow up SUSARs until resolution or until, in the opinion of the investigator, the events are stabilized or determined to be chronic.

9.4 APPENDIX 4: STUDY GOVERNANCE

9.4.1 Data Quality Assurance

This study will be conducted using the quality processes described in applicable procedural documents. The quality management approach to be implemented will be documented and will comply with current ICH guidance on quality and risk management. All aspects of the study will be monitored for compliance with applicable government regulatory requirements, current GCP, the protocol, and standard operating procedures. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. Electronic CRFs and electronic data capture will be utilized. The electronic data capture system is validated and compliant with the applicable regulatory requirements. Each person involved with the study will have an individual identification code and password that allows for record traceability.

Important protocol deviations, should they occur during the study, will be presented in Section 10.2 of the clinical study report.

9.4.2 Investigator Obligations

The following administrative items are meant to guide the investigator in the conduct of the study and may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IEC but will not result in protocol amendments.

9.4.2.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, the EMA / FDA or any other regulatory agency, or the IEC.

The investigators and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the

study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

9.4.2.2 Ethics Committee Review

Local regulations and ICH guidelines require that approval be obtained from an IEC before participation of human subjects in research studies. Before study onset, the protocol, ICF, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study that is to be provided to the subject must be approved by the IEC. Documentation of all IEC approvals and of the IEC compliance with the ICH harmonised tripartite guideline E6(R2): Good Clinical Practice will be maintained by the sites and will be available for review by the sponsor or its designee.

All IEC approvals should be signed by the IEC chairman or designee and must identify the IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

9.4.2.3 Subject Consent

Written informed consent in compliance with the applicable regulatory requirements, GCP and ICH shall be obtained from each subject before he enters the study or before performing any unusual or nonroutine procedure that involves risk to the subject. If any institution-specific modifications to study-related procedures are proposed or made by the sites, the consent should be reviewed by the sponsor or its designee or both before IEC submission. Once reviewed, the investigator will submit the ICF to the IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating subjects must sign the revised form.

Before recruitment and enrollment, each prospective subject will be given a full explanation of the study and will be allowed to read the approved ICF. The investigator or designated personnel will inform the subject of the objectives, methods, anticipated benefits, and potential risks and inconveniences of the study. The subject will be given every opportunity to ask for clarification of any points he does not understand and, if necessary, ask for more information. At the end of the interview, the subject will be given ample time to consider the study. Once the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give his or her consent to participate in the study by signing and dating the ICF. After signatures are obtained, the ICF will be archived by the investigator in the investigator's study file. A copy of the ICF will be provided to the subject.

It will be emphasized that the subject may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent will not be included or continue to participate in the study. The investigators will be responsible for ensuring that no subject undergoes any study related examination or procedure before he has signed the informed consent to participate in the study.

9.4.2.4 Study Reporting Requirements

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in this protocol. In addition, the investigator agrees that PPD will submit annual reports to the IEC as appropriate, on the investigator's behalf.

9.4.2.5 Financial Disclosure and Obligations

The investigator is required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under EMA, FDA, or any other regulatory agency and to comply with ICH E6(R2) Section 8.2. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor PPD is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor PPD is financially responsible for further treatment of the disease under study.

9.4.2.6 Investigator Documentation

Prior to beginning the study, the investigators will be asked to comply with ICH E6(R2) Section 8.2, US Title 21 of the CFR and all other applicable regulatory requirements by providing essential documents, including but not limited to, the following:

- IEC approval
- An original investigator-signed investigator agreement page of the protocol
- Curriculum vitae for the principal investigators and each subinvestigator. Current licensure must be noted on the curriculum vitae. Curriculum vitae will be signed and dated by the

principal investigators and subinvestigators at study start-up, indicating that they are accurate and current.

- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under EMA, FDA, or any other regulatory agency and to comply with ICH E6(R2) Section 8.2. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.

- An IEC-approved ICF, samples of site advertisements for recruitment for this study, and any other written information about this study that is to be provided to the subject

- Laboratory certifications and reference ranges for any local laboratories used by the site, in accordance with the applicable regulatory requirements

9.4.2.7 Study Conduct

The investigators agree to perform all aspects of this study in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH E6(R2): Good Clinical Practice; the protocol; and all national, state, and local laws or regulations.

9.4.2.8 Case Report Forms and Source Documents

Site personnel will maintain source documentation, enter subject data into the eCRF as accurately as possible, and will rapidly respond to any reported discrepancies.

Electronic CRFs and electronic data capture will be utilized. The electronic data capture system is validated and compliant with the applicable regulatory requirements. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and any subsequent investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records, as well as the time and date of any modifications. There may be an internal quality review audit of the data and additional reviews by the clinical monitor.

Each eCRF is presented as an electronic copy, allowing data entry by site personnel, who can add and edit data, add new subjects, identify and resolve discrepancies, and view records. This system provides immediate direct data transfer to the database, as well as immediate detection

of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner.

Paper copies of the eCRFs and other database reports may be printed and signed by the investigator. This system provides site personnel, monitors, and reviewers with access to hardcopy audits, discrepancy reviews, and investigator comment information. Following all data validation steps, the investigator (or designee) will electronically sign the completed electronic data prior to database lock.

9.4.2.9 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol, in accordance with ICH E6(R2) and all applicable guidelines and regulations.

9.4.2.10 Reporting Adverse Events

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in this protocol. In addition, the investigator agrees that PPD will submit annual reports to the IEC as appropriate, on the investigator's behalf. The investigator also agrees that PPD will provide the sponsor with an adequate report, if applicable, shortly after completion of the investigator's participation in the study.

9.4.2.11 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IEC with a summary of the study's outcome and the sponsor and regulatory authorities with any reports required.

9.4.2.12 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the sponsor. The sponsor is responsible for informing the investigator/institution when these documents no longer need to be retained.

Records and documents including the signed ICF, pertaining to the conduct of this study must be retained and archived at the study site for at least 25 years after the end of the study. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

9.4.2.13 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and any other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without their prior authorisation, but data and any publication thereof will not be unduly withheld.

9.4.3 Study Management

9.4.3.1 Monitoring

9.4.3.1.1 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, is obligated to follow the study closely. In doing so, the monitor will visit the investigators and study sites at periodic intervals in addition to maintaining necessary telephone and email contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigators and staff.

PPD will designate a blinded and an unblinded study monitor who will be responsible for monitoring this clinical study. The study monitors will monitor the study conduct, eCRF and source documentation completion and retention, and accurate study drug accountability. To this end, the study monitors will visit the study sites at suitable intervals and be in frequent contact through verbal and written communication. It is essential that the study monitors have access to all documents, related to the study and the individual subjects, at any time these are requested. In turn, the study monitors will adhere to all requirements for subject confidentiality as outlined in the ICF. The investigators and investigators' staff will be expected to cooperate

with the study monitors, to be available during a portion of the monitoring visit to answer questions, and to provide any missing information.

All aspects of the study will be carefully monitored by the sponsor or its designee for compliance with applicable government regulation with respect to current ICH E6(R2) guidelines and standard operating procedures.

9.4.3.1.2 Inspection of Records

The investigators and institutions involved in the study will permit study-related monitoring, audits, IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigators agree to allow the sponsor, their representatives, the FDA, EMA, or other regulatory agencies access to all study records.

The investigators should promptly notify the sponsor and study site(s) of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

9.4.3.2 Management of Protocol Amendments and Deviations

9.4.3.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent immediate hazard to the subject, must be reviewed and approved by the sponsor or designee. Amendments to the protocol must be submitted in writing to the investigator's IEC for approval before subjects are enrolled into an amended protocol.

9.4.3.2.2 Protocol Deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to study subjects without prior IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. An important deviation (sometimes referred to as a major

or significant deviation) is a subset of protocol deviations that leads to a subject being discontinued from the study, or significantly affects the subject's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the study data. An important deviation can include nonadherence to inclusion or exclusion criteria or nonadherence to FDA or other regulatory agency regulations or ICH E6(R2) guidelines.

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. The investigator will be notified in writing by the monitor of deviations. The IEC should be notified of all major protocol deviations, if appropriate, in a timely manner.

9.4.3.3 Study Termination

Although the sponsor has every intention of completing the study, they reserve the right to discontinue it at any time for clinical (eg, important AEs, SAEs, SUSARs reported), ethical, or administrative reasons (eg, low recruitment).

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

- A SUSAR of the same nature (meaning an SAE considered both unexpected and at least possibly related to the study drug administration) occurs in more than 2 subjects.
- A severe and clinically significant nonserious adverse reaction of the same nature (meaning a severe nonSAE considered at least possibly related to the study drug administration) occurs in more than 2 subjects.

The end of the study is defined as the date on which the last subject completes the last visit (including the EOS visit and any additional long-term follow-up). Any additional long-term follow-up that is required for monitoring of the resolution of an AE or finding may be appended to the clinical study report.

9.4.3.4 Final Report

Regardless of whether the study is completed or prematurely terminated, the sponsor will ensure that clinical study reports are prepared and provided to regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review complete study results.

Upon completion of the clinical study report, the investigator(s) will be provided with the final approved clinical study report, as appropriate.