Clinical Study Protocol with Amendment 02

Study Number TVB009-IMB-30085

A Randomized, Double-Blind, Multinational, Multicenter Study to Compare Efficacy, Safety, and Immunogenicity of TVB-009P and Denosumab (PROLIA®[1]) in Patients with Postmenopausal Osteoporosis

Short title: **A Randomized, Double-Blind Study on Efficacy, Safety, and Immunogenicity of TVB-009P in Adults with Postmenopausal Osteoporosis**

Title of the protocol for lay people: **A Study to Test if TVB-009P is Effective in Relieving Postmenopausal Osteoporosis**

Efficacy and Safety Study (Phase 3)

IND number: 137313; EudraCT number: 2020-005548-48

EMA Decision number of Pediatric Investigation Plan: Not applicable

Article 45 or 46 of 1901/2006 does not apply

Protocol with Amendment 02

Version Date: 29 June 2021

Sponsor
Teva Branded Pharmaceutical
Products R&D, Inc.
145 Brandywine Parkway
West Chester, PA 19380
United States of America

Information regarding clinical laboratories and other departments and institutions is found in Appendix A

This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Council for Harmonisation (ICH); United States (US) Code of Federal Regulations (CFR), and European Union (EU) Directives and Regulations (as applicable in the region of the study); national country legislation; and the sponsor's Standard Operating Procedures (SOPs).

Confidentiality Statement

[1] PROLIA is a registered trademark of Amgen, Inc.

AMENDMENT HISTORY

The protocol for study TVB009-IMB-30085 (original protocol dated 09 December 2020) has been revised and reissued as follows:

Amendment 01	03 February 2021 No patients enrolled to date
Local Amendment 01 for Germany	19 May 2021 No patients enrolled to date
Amendment 02	29 June 2021 14 patients enrolled to date

The Summary of Changes to the Protocol includes the corresponding reason/justification for each change and is provided in Section 16.

SPONSOR PROTOCOL APPROVAL

Clinical Study Protocol with Amendment 02

Study TVB009-IMB-30085

A Randomized, Double-Blind, Multinational, Multicenter Study to Compare Efficacy, Safety, and Immunogenicity of TVB-009P and Denosumab (PROLIA®) in Patients with Postmenopausal Osteoporosis

Version Date: 29 June 2021

I have read the protocol with Amendment 02 and approve the design of this study.

Sponsor's Authorized Representative	**Signature**	**Date**
[redacted]		

Executed signature pages are maintained separately within the Trial Master File

INVESTIGATOR AGREEMENT

Clinical Study Protocol with Amendment 02

Study TVB009-IMB-30085

A Randomized, Double-Blind, Multinational, Multicenter Study to Compare Efficacy, Safety, and Immunogenicity of TVB-009P and Denosumab (PROLIA®) in Patients with Postmenopausal Osteoporosis

Version Date: 29 June 2021

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel: _____

I have read the protocol with Amendment 02 and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. The signature below constitutes agreement with this protocol and attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to national or local legal and regulatory requirements and applicable regulations and guidelines.

I will make available the protocol and all information on the investigational medicinal product (IMP) that were furnished to me by the sponsor to all physicians and other study personnel reporting to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the IMP and the conduct of the study. I agree to keep records on all patient information, IMP shipment and return forms, and all other information collected during the study, in accordance with national and local GCP regulations as well as all other national and international laws and regulations.

Principal Investigator	**Signature**	**Date**

Executed signature pages are maintained separately within the Trial Master File

COORDINATING INVESTIGATOR AGREEMENT

Clinical Study Protocol with Amendment 02

Study TVB009-IMB-30085

A Randomized, Double-Blind, Multinational, Multicenter Study to Compare Efficacy, Safety, and Immunogenicity of TVB-009P and Denosumab (PROLIA®) in Patients with Postmenopausal Osteoporosis

Version Date: 29 June 2021

Coordinating Investigator: [redacted]

Title: [redacted]

Address of Investigational Center: [redacted]

Tel: _____

I have read the protocol with Amendment 02 and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. The signature below constitutes agreement with this protocol and attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to national or local legal and regulatory requirements and applicable regulations and guidelines.

I will make available the protocol and all information on the IMP that were furnished to me by the sponsor to all physicians and other study personnel reporting to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the IMP and the conduct of the study. I agree to keep records on all patient information, IMPs shipment and return forms, and all other information collected during the study, in accordance with national and local GCP regulations as well as all other national and international laws and regulations.

Coordinating Investigator	Signature	Date
[redacted]		

Executed signature pages are maintained separately within the Trial Master File

CLINICAL STUDY PROTOCOL SYNOPSIS

With Amendment 02

Study TVB009-IMB-30085

Title of Study: A Randomized, Double-Blind, Multinational, Multicenter Study to Compare Efficacy, Safety, and Immunogenicity of TVB-009P and Denosumab (PROLIA®) in Patients with Postmenopausal Osteoporosis

Sponsor: Teva Branded Pharmaceutical Products R&D, Inc.

Investigational New Drug (IND) Number: 137313 **New Drug Application (NDA) Number:** na **Biologics License Application (BLA) Number:** na **European Drug Regulatory Authorities Clinical Trials (EudraCT) Number:** 2020-005548-48

European Medicines Agency (EMA) Decision number of Pediatric Investigation Plan: Article 45 or 46 of 1901/2006 does not apply

Name of Investigational Medicinal Products (IMP): Test IMP: TVB-009 (denosumab) solution for injection 60 mg/mL (1 mL) prefilled syringe (PFS) (TVB-009P). Reference IMP: PROLIA United States (US) (denosumab) solution for injection 60 mg/mL (1 mL) PFS.

EudraVigilance (EV) code for the IMP, if applicable: Not applicable

Type of Study: Efficacy and safety (Phase 3)

Indication: Postmenopausal osteoporosis (PMO)

Is this study conducted to investigate the New Use of an approved, marketed product? No

Number of Investigational Centers Planned: The study is planned to be conducted in approximately 75 investigational centers

Countries Planned: The study is planned to be conducted in approximately 10 countries

[redacted]

Number of Patients Planned (total): Approximately 326 patients (163 per arm) will be randomized to achieve approximately [redacted] at the end of the main 52-week treatment period.

Study Population: Female adult patients with PMO ≥60 and ≤90 years of age

Primary and Secondary Objectives and Endpoints: The objectives of this study are to demonstrate that there are no clinically meaningful differences in efficacy, safety, and immunogenicity between TVB-009P and PROLIA US administered subcutaneously (sc) in patients with PMO. The primary and secondary study objectives and endpoints are presented below.

Primary and Secondary Study Objectives and Endpoints

Objectives	Endpoints
The **primary objective** of the study is to demonstrate that there are no clinically meaningful differences in efficacy between TVB-009P and PROLIA US administered subcutaneously in patients with postmenopausal osteoporosis.	The primary efficacy endpoint is • the percent change from baseline in lumbar spine-bone mineral density (LS-BMD) at week 52 based on centrally assessed dual-energy X-ray absorptiometry (DXA) measurements • The co-primary efficacy endpoint for the European Union (EU) submission is the percent change from baseline in serum C-telopeptide cross-link of type 1 collagen (sCTX-1) at week 26. For the EU submission, this endpoint is regarded as co-primary. For the United States (US) submission, this endpoint is regarded as secondary
A **secondary objective** is to compare further efficacy and pharmacodynamic parameters between TVB-009P and PROLIA US.	The secondary efficacy and pharmacodynamic endpoints are: • percent change from baseline in LS-BMD at week 26 based on centrally assessed DXA measurements • percent change from baseline in femoral neck bone mineral density (BMD) by DXA at week 26 and at week 52 • percent change from baseline in total hip BMD by DXA at week 26 and at week 52 • percent change from baseline in sCTX-1 at all time points • sCTX-1 suppression at week 4 • percent change from baseline in procollagen type 1 N propeptide (P1NP) at week 26 and week 52 • incidence of fractures up to week 52
A **secondary objective** of the study is to compare efficacy and pharmacodynamic parameters between TVB-009P and PROLIA US after a single transition from PROLIA US to TVB-009P.	The pharmacodynamic/efficacy endpoints in the transition period are: • percent change from week 52 in LS-BMD by DXA at week 78 • difference between percent change from baseline in sCTX-1 between week 52 and week 78 • percent change from week 52 in femoral neck BMD by DXA at week 78 • percent change from week 52 in total hip BMD by DXA at week 78 • difference between percent change from baseline in P1NP between week 52 and week 78 • incidence of fractures up to week 78
A **secondary objective** of this study is to compare the safety and tolerability, including device-related events, between TVB-009P and PROLIA US throughout the study. A **secondary objective** of this study is to compare the safety and tolerability between TVB-009P and PROLIA US after a single transition from PROLIA US to TVB-009P, including device-related events.	The safety and tolerability endpoints are: • adverse events (and the number of patients who withdraw from the study due to adverse events) • vital signs • laboratory tests (hematology, serum chemistry, and urinalysis) • electrocardiogram (ECG) • local tolerability at injection site • use of concomitant medications • device-related adverse events and malfunctions
A **secondary objective** of this study is	The immunogenicity endpoint is:

Objectives	Endpoints
to assess the immunogenicity of TVB-009P in comparison with PROLIA US throughout the study. A **secondary objective** of this study is to assess the immunogenicity of TVB-009P in comparison with PROLIA US after a single transition from PROLIA US to TVB-009P.	• incidence of patients with confirmed positive anti-drug antibody (ADA) sample For confirmed positive samples, the ADA titer and the neutralizing potential will be tested. The effect of positive immunogenicity findings on pharmacokinetics, efficacy, and safety will be assessed if applicable.

Exploratory Objectives and Endpoints

Objectives	Endpoints
An **exploratory objective** of this study is to compare pharmacokinetics between TVB-009P and PROLIA US throughout the study.	The pharmacokinetic endpoints are: • serum concentration before next dose (C_{trough}), before second and third dose, and 6 months after third dose • serum concentration at 2 weeks postdose (C_{2weeks}) Pharmacokinetic endpoints derived from population pharmacokinetics analysis are: • area under the curve over the dosing period ($AUC_{0\text{-}tau}$) after first dose • C_{trough} before second dose • maximum observed concentration (C_{max}) after first dose

Primary Estimand:

The primary estimand assesses clinically meaningful differences in effectiveness in patients with PMO, based on surrogate measures, focusing on the causal effects attributable to the IMP.

The primary estimand is the difference in mean percent change in lumbar spine-bone mineral density (LS-BMD) from baseline at week 52 between TVB-009P and PROLIA US treatment arms, regardless of intercurrent events, in the target population of patients with PMO who receive at least one dose of IMP and have both a baseline and at least 1 post-baseline assessment of LS-BMD. For the submission in the US, this estimand is regarded as primary and for the submission in the European Union (EU), this estimand is regarded as co-primary.

The co-primary estimand for the EU filing is the difference in mean percent change in serum C telopeptide cross link of type 1 collagen (sCTX-1) from baseline at week 26, between TVB-009P and PROLIA US treatment arms, regardless of intercurrent events in the target population of patients with PMO. The same analysis set will be used for both estimands and therefore patients who terminate before week 26 will not be included in the sCTX-1 analysis. For the EU submission, this estimand is regarded as co-primary. For the US submission, this estimand is regarded as secondary.

General Study Design: This is a multinational, multicenter, randomized, double-blind study to demonstrate similar efficacy and safety of TVB-009P compared to PROLIA US over 78 weeks administered sc at doses of 60 mg every 26 weeks (3 injections) in patients with PMO.

This study will consist of 3 periods:

- screening period of up to 4 weeks
- double-blind main treatment period of 52 weeks
- double-blind transition period of 26 weeks

After informed consent is obtained, eligibility criteria will be reviewed and screening evaluations will be performed.

At baseline, patients will be randomized in a 1:1 ratio to receive the first 2 doses of TVB-009P or PROLIA US ("main treatment period"). The first dose of TVB-009P or PROLIA US will be administered following randomization. The second dose will be administered 26 weeks after the first dose.

At week 52 (26 weeks after the second dose and prior to receiving their third dose), patients in the PROLIA US arm will be re-randomized 1:1 to either continue with a third dose of PROLIA US or transition to TVB-009P and receive a single dose of TVB-009P in the transition period to assess primarily immunogenicity and safety after a transition from PROLIA US to TVB-009P. All patients in the TVB-009P group will continue treatment with a third dose of TVB-009P. All patients who do not terminate the study before the third dose will be followed for 26 weeks after the third dose of study drug.

Final procedures and assessments will be performed at the end of study (EOS) visit at the end of the 78-week study period. Patients who withdraw from the study before completing the 78-week study period will have early termination (ET) procedures and assessments performed at their final visit. A patient who is randomized but does not complete all treatment periods will not be replaced. In case the assessment of LS-BMD is missing or not evaluable from more than 10% of the patients at the week 26 visit, the sponsor may decide to continue the recruitment of patients in order to increase the number of evaluable patients.

The safety of TVB-009P and PROLIA US will be assessed throughout the study by evaluating adverse events, device-related adverse events and malfunctions, clinical laboratory test results, vital signs measurements, ECG findings, physical examination results, local tolerability at the injection site, and concomitant medication usage.

Method of Randomization and Blinding: This is a randomized, double-blind study. At baseline, patients will be randomized in a 1:1 ratio to receive the first 2 doses of TVB-009P or PROLIA US ("main treatment period") at day 1 and week 26. [redacted] At week 52, prior to receiving their third dose of study medication, patients in the PROLIA US treatment group will be re-randomized in a 1:1 ratio to continue with a third dose of PROLIA US or switch to TVB-009P ("transition period") and receive a single dose of TVB-009P. [redacted] All patients in the TVB-009P group will receive a third dose of TVB-009P at week 52.

During the main treatment period, the sponsor, investigators (and other site staff involved in study assessments) and patients will be blinded to the treatment assignment of all patients. To maintain blinding of the patients and investigators (and other site staff involved in study assessments) to the treatment assignment of all patients during the entire study, and maintain

blinding of the sponsor until the main treatment period is unblinded, the re-randomization process will be performed for all patients, including the patients in the TVB-009P group.

Investigational Medicinal Products: Dose, Pharmaceutical Form, Route of Administration, and Administration Rate

IMP name		**Test IMP**	**Reference IMP**
Trade name or company-assigned number		TVB-009P	PROLIA US
Formulation	Active	60 mg/mL	60 mg/mL
	Acetate	17 mM	17 mM
	Sorbitol	4.7%	4.7%
	Polysorbate 20	0.01%	0.01%
	Sodium hydroxide	pH to 5.2	pH to 5.2
	Water for injection	qs to 1 mL	qs to 1 mL
Unit dose strength(s)/Dosage level(s)		60 mg/mL 60 mg/dose	60 mg/mL 60 mg/dose
Route of administration		sc injection	sc injection
Device		Automatically activated needle safety guard	Manually activated needle safety guard
Manufacturer		Teva Branded Pharmaceutical Products R&D, Inc., West Chester, Pennsylvania, USA	Amgen Inc., One Amgen Center Drive, Thousand Oaks, California 91320-1799, USA
Storage conditions		2°C to 8°C (36°F to 46°F), protected from direct light and heat. Avoid vigorous shaking	2°C to 8°C (36°F to 46°F), protected from direct light and heat. Avoid vigorous shaking

IMP=investigational medicinal product; PFS=prefilled syringe; qs=quantum satis; sc=subcutaneous; US=United States; USA=United States of America

Duration of Patient Participation and Maximal Exposure to IMP: The total duration of patient participation in the study is planned to be approximately 82 weeks including up to an approximate 4-week screening period, approximately a 52-week double-blind main treatment period, and an approximately 26-week double-blind transition period. Patients will receive a maximum of three injections of 60 mg denosumab.

End of Study: EOS is defined as the last visit of the last patient of the transition period.

Plans for Treatment or Care after the Patient Has Ended Participation in the Study: After study end, no IMP will be provided as PROLIA is commercially available.

Selection of Patients/Study Population

Inclusion Criteria: Patients may be included in this study only if they meet all of the following criteria:

a. The patient provides a signed and dated written informed consent.

b. The patient is a clinically stable, ambulatory, female postmenopausal adult (≥60 and ≤90 years) with a diagnosis of osteoporosis.

c. The patient is of postmenopausal status, defined as:
   - Spontaneous amenorrhea for >12 months, or
   - Spontaneous amenorrhea >6 months and serum follicle stimulating hormone (FSH) and estradiol (E2) in menopausal range, or
   - Surgical menopause at least 6 weeks before the start of screening.

d. The patient has a body weight ≥50 kg and ≤90 kg (≥110 lb and ≤198 lb) at screening.

e. The patient agrees to be supplemented with 1000 mg calcium and at least 400 IU vitamin D daily from screening until the last visit.

f. The patient has a bone mineral density (BMD)-measurement T-score of less than -2.5 but not less than -4.0 by dual energy X-ray absorptiometry (DXA) at the lumbar spine at screening based on central reader assessment.

g. The patient has at least 3 (three) vertebrae in the L1-L4 region that are evaluable by DXA.

h. The patient has serum 25 (OH) vitamin D level >20 ng/mL at screening and no current hyper- or hypocalcemia, defined as albumin-adjusted serum calcium outside the normal range, as assessed by the central laboratory. Vitamin D and calcium supplements will be provided and patients may be rescreened once to re-evaluate calcium and/or vitamin D level post repletion.

i. The patient must be willing and able to comply with study restrictions and to remain at the investigational center for the required duration during the study period, and willing to return to the investigational center for further visits, as applicable, and the follow-up procedures and assessments as specified in this protocol.

Exclusion Criteria: Patients will be excluded from participating in this study if they meet any of the following criteria:

a. The patient has a known malabsorption of calcium or vitamin D supplements.

b. The patient has a metabolic or bone disease (except osteoporosis) such as Paget's disease, Cushing's disease, rheumatoid arthritis, sclerosteosis, osteomalacia, osteogenesis imperfecta, osteopetrosis, ankylosing spondylitis, hyperprolactinemia, malabsorption syndrome, osteomyelitis, multiple myeloma or related lymphoproliferative disorder, or bone metastases.

c. The patient has a current, uncontrolled hyperthyroidism or hypothyroidism, per patient report or chart review.

d. The patient has hypoparathyroidism or hyperparathyroidism (irrespective of current controlled or uncontrolled status).

e. The patient has a history and/or presence of risk factors of osteonecrosis of the jaw, as determined by the principal investigator, (eg, unhealed open soft tissue lesions in the mouth, poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, recent or planned invasive dental procedures such as tooth extractions

within the next 18 months), presence of anemia or coagulopathy at screening, and/or inability to maintain oral hygiene during the study.

f. The patient has a history and/or presence of 1 severe or more than 2 moderate vertebral fractures (as determined by central reading of lateral spine X-ray during the screening period).

g. The patient has a history and/or presence of hip fracture or atypical femur fracture.

h. The patient has participated in another study of an IMP (or a medical device) within the previous 30 days or 5 half-lives of the IMP (whichever is longer) or longer if required by local regulations, or is currently participating in another study of an IMP (or a medical device).

i. The patient has a known hypersensitivity to any components of the IMPs stated in this protocol or to calcium or vitamin D.

j. The patient has a renal impairment manifested with an estimated glomerular filtration rate (eGFR) <45 mL/min.

k. The patient has cardiac disease as per investigator's discretion, including electrocardiogram (ECG) abnormalities at screening indicating significant risk of safety for patients participating in the study.

l. The patient has a malignancy or past malignancy (except for local non-melanoma skin cancer fully resected).

m. The patient has a current skin infection(s).

n. The patient has infectious disease:

   – Acute infection and/or antibiotic treatment must be resolved 28 days prior to the first dose of IMP.

   – Any relevant chronic infection.

   – Ongoing hepatitis B, hepatitis C, human immunodeficiency virus (HIV) Types 1 or 2 infection.

   – Positive test for coronavirus disease 2019 (COVID-19) during screening or patient reporting a recent history of confirmed COVID-19 which had not fully recovered more than 14 days before screening.

o. The patient has any medical condition that (treated or untreated), in the opinion of the investigator, could jeopardize or would compromise the patient’s safety or ability to participate in this study.

p. The patient has had any prior treatment with denosumab (PROLIA or XGEVA or biosimilars of denosumab products).

q. The patient has used intravenous bisphosphonates within less than 5 years prior to screening.

r. The patient has used oral bisphosphonates within the 12 months prior to start of screening and/or cumulative use >3 years before the start of screening.

s. The patient has ongoing use of any osteoporosis treatment (other than calcium and vitamin D supplements). The following rules for prior use of osteoporosis treatments have to be adhered to:

   - Drugs being investigated for osteoporosis, eg romosozumab: dose received at any time.
   - Strontium or fluoride (for osteoporosis): dose received at any time.
   - Teriparatide or any parathyroid hormone (PTH) analogs: dose received within 12 months before the start of screening.
   - Calcitonin: dose received within 6 months before the start of screening.
   - Cinacalcet: dose received within 3 months before the start of screening.

t. The patient has ongoing use of any bone active drugs which can affect BMD including:

   - Heparin (except topical), anti-convulsives (with the exception of benzodiazepines), systemic ketoconazole, adrenocorticotropic hormone, lithium, gonadotropin releasing hormone agonists, or anabolic steroids; dose received within 3 months before the start of screening.
   - Systemic glucocorticosteroids: total cumulative dose of ≥50 mg within 3 months prior to randomization.
   - Systemic oral or transdermal estrogen or selective estrogen receptor modulators: more than 1 month of cumulative use within 6 months prior to randomization.

u. The patient is a pregnant or lactating woman, or plans to become pregnant during the study.

v. The patient has a history of chronic alcohol or drug abuse within the previous 6 months.

w. The patient is vulnerable (eg, people kept in detention).

Statistical Considerations

Sample Size Rationale: [redacted].

Primary Efficacy Analysis: The primary analysis of LS-BMD percent change from baseline at week 52 is an analysis of covariance (ANCOVA) model [redacted] Similarity will be demonstrated if the 95% CI for the mean difference between TVB-009P and PROLIA US falls entirely within the similarity margin of ±1.45%.

The primary analysis of sCTX-1 percent change from baseline at week 26 is an ANCOVA model [redacted]. Values below limit of quantitation (BLQ) will be imputed as the lower limit of quantification (LLOQ). Similarity will be demonstrated if the 95% CI for the mean difference between TVB-009P and PROLIA US falls entirely within the similarity margin of ±20%.

Patients who withdraw from the study prior to week 26 will not have a post-baseline LS-BMD measurement, and will therefore not be included in the modified intent-to-treat (mITT) analysis set. For patients who withdraw from the study between week 26 and week 52 and have an LS-BMD measurement at week 26 and/or ET, the percent change from baseline in LS-BMD at week 52 will be imputed using the predictive mean matching multiple imputation method, for each treatment arm separately. The resulting complete, imputed datasets will be analyzed using Rubin's multiple imputation methodology.

Sensitivity/Supportive Analyses: To assess the robustness of the primary efficacy analysis, sensitivity and supportive analyses will include repeating the primary analysis model including only treatment group as a covariate; repeating the primary analysis on the ITT analysis set; and two-dimensional tipping-point. Additional sensitivity and supportive analyses will be conducted.

Efficacy Analysis in the Transition Period: No formal statistical analysis of efficacy endpoints in the transition period is planned; descriptive statistics will be presented.

Multiple Comparisons and Multiplicity: Formal statistical analysis of similarity will be performed only on the following endpoints:

(1) percent change from baseline to week 52 in LS-BMD

(2) percent change from baseline in sCTX-1 at week 26

For the US filing, percent change from baseline to week 52 in LS-BMD is the primary endpoint.

For the EU submission, percent change from baseline in LS-BMD at week 52 and percent change from baseline in sCTX-1 at week 26 are co-primary endpoints. For this submission, success will be declared if similarity is demonstrated for both co-primary endpoints.

The analysis of all other endpoints will be descriptive, therefore no control for multiplicity is needed.

Safety Analyses: All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Each patient will be counted only once in each preferred term (PT) or system organ class (SOC) category for the analyses of safety. Patient listings of all adverse events, serious adverse events, and adverse events leading to withdrawal will be presented.

For continuous variables, descriptive statistics will be provided for actual values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided.

If any patient dies during the study, a listing of deaths will be provided and all relevant information will be discussed in the patient narrative included in the clinical study report (CSR).

Tolerability Analysis: If more than 10% of the patients withdraw from the study before the end of the main treatment period, the number of days until study discontinuation will be analyzed using Kaplan-Meier methodology.

Pharmacokinetic Analysis: The following exploratory pharmacokinetic parameters will be summarized using descriptive statistics:

- serum concentration before next dose (C_{trough}), before second and third dose, and 6 months after third dose
- serum concentration at 2 weeks postdose (C_{2weeks})

Details of the pharmacokinetic analysis of the area under the curve over the dosing period ($AUC_{0\text{-}tau}$) after first dose derived from population pharmacokinetics analysis, C_{trough} before second dose derived from population pharmacokinetics analysis, and maximum observed concentration (C_{max}) after first dose derived from population pharmacokinetic analysis will be given in a separate TVB-009P population pharmacokinetic statistical analysis plan. The results of the population pharmacokinetic analysis will be provided in a separate report.

Immunogenicity Analysis: The immunogenicity analysis of TVB-009P, PROLIA US and PROLIA US/TVB-009P treatment groups will be performed after completion of the main treatment period at week 52 and after the completion of the transition period at week 78 (EOS).

Results of immunogenicity assessment will be listed. If more than 5 patients develop anti-drug antibody (ADA) anytime post-baseline, the incidence of ADA positive patients will be summarized by treatment group, and ADA status (positive/negative), titer level, and neutralizing ADA positive/negative will be summarized at each visit using descriptive statistics. The effect of positive immunogenicity findings on efficacy and safety may be investigated, if applicable.

Sequence of Final Analyses: Upon completion of the main treatment period the sponsor will unblind the main treatment period (up to and including week 52; not including third IMP dose and assessments following the third dose), while keeping the investigators (and other site staff involved in study assessments) and the patients blinded. A CSR that contains the results of the analysis of the main treatment period (up to and including week 52) will be submitted with the filing of the Marketing Authorisation Application (MAA) and/or the Biologics License Application (BLA). The results of the analysis of the transition period (up to and including week 78) will be included in a CSR addendum that is planned to be submitted in the BLA or during the 4-Month Safety Update after filing of the BLA and at the earliest opportunity during the MAA procedure.

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Abbreviation	Term
Ab	antibodies
ADA	anti-drug antibody
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
$AUC_{0\text{-}tau}$	area under the curve over the dosing period
BLA	Biologics License Application
BLQ	below limit of quantitation
BMD	bone mineral density
BP	blood pressure
C_{2weeks}	serum concentration at 2 weeks postdose
CDC	complement dependent cytotoxicity
CDMS	clinical data management system
CFR	Code of Federal Regulations (USA)
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum observed concentration
COVID-19	coronavirus disease 2019
CRF	case report form (refers to any media used to collect study data [ie, paper or electronic])
CRO	Contract Research Organization
CSR	Clinical Study Report
C_{trough}	serum concentration before next dose
DBL	database lock
DNA	deoxyribonucleic acid
DXA	dual-energy X-ray absorptiometry
E2	estradiol
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOM	end of main treatment period
EOS	end of study

Abbreviation	Term
ET	early termination
EU	European Union
EudraCT	European Drug Authorities Clinical Trials
Fab	antigen-binding fragment
Fc	crystallizable fragment
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GBT	Biologics, Assays & Technology
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GPSP	Global Patient Safety and Pharmacovigilance
GCA	Global Quality Assurance
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HEENT	head, eyes, ears, nose, and throat
IB	Investigator's Brochure
ICF	informed consent form
ICH	The International Council on Harmonisation
IEC	Independent Ethics Committee
IgG2	immunoglobulin G2
IMP	investigational medicinal product
IND	Investigational New Drug
INN	international nonproprietary name
IRB	Institutional Review Board
ITT	intent-to-treat
iv	intravenous
LLOQ	lower limit of quantification
LS-BMD	Lumbar spine-bone mineral density
LSO	local safety officer
MAA	Marketing Authorisation Application
mAb	monoclonal antibody
MAR	missing at random
MDRD	Modification of Diet in Renal Disease

Abbreviation	Term
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MNAR	missing not at random
n	number
NRS-11	11-point pain intensity numerical response scale
OH	hydroxy
ONJ	osteonecrosis of the jaw
P1NP	procollagen type 1 N propeptide
PEF	peak expiratory flow
PFS	pre-filled syringe
PI	Prescribing Information
PMO	postmenopausal osteoporosis
PP	per-protocol
PT	preferred term
PTH	parathyroid hormone
qs	quantum
RANK	receptor activator of nuclear factor kappa-B
RANKL	receptor activator of nuclear factor kappa-B ligand
RSI	reference safety information
RTSM	Randomization and Trial Supply Management
SMP	SAE Management Plan
SAP	statistical analysis plan
sc	subcutaneous/ly
sCTX-1	serum C-telopeptide cross-link of type 1 collagen
SD	standard deviation
SERM	selective estrogen receptor modulator
SOC	system organ class
SOP	standard operating procedure
SPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reaction
TmITT	transition modified intent-to-treat
ULN	upper limit of normal
US	United States
USA	United States of America

Abbreviation	Term
USPI	United States Prescribing Information
V	visit
VC	videoconference
W	week
WHO	World Health Organization
WHODrug	World Health Organization Drug Dictionary
XML	Extensible Markup Language

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Introduction

1.1.1. TVB-009

TVB-009 is a fully human immunoglobulin G2 (IgG2)/kappa monoclonal antibody (mAb) directed against receptor activator of nuclear factor kappa-B ligand (RANKL), which is being developed by Teva as a biosimilar candidate to PROLIA[2] and XGEVA[3] with the active substance denosumab. Denosumab is currently licensed as PROLIA and XGEVA, both being first approved in the US in 2010, and in the EU in 2010 (PROLIA) and 2011 (XGEVA). TVB-009 has been engineered by the development of deoxyribonucleic acid (DNA) vectors encoding a protein that is 100% identical to the amino acid sequence of denosumab heavy and light chains.

Biosimilarity assessment results, from functional assays of both the antigen-binding fragment (Fab) and crystallizable fragment (Fc) domain-related activity, demonstrate that TVB-009 values were generally in the range or similar to US-licensed PROLIA reference product for all critical product parameters related to the denosumab mechanism of action. Minor differences were observed in the disulfide isoform distribution, and complement dependent cytotoxicity (CDC) activity but these differences were not considered to be clinically meaningful. Analytical (structural and functional) evaluation demonstrates TVB-009 similarity to PROLIA based on substantial data, risk assessment and totality of evidence approach.

Several molecular signals are involved in regulating bone resorption by osteoclasts and bone formation by osteoblasts during the process of normal bone remodeling. In particular, RANKL is a key activator of osteoclasts. Binding to its receptor, receptor activator of nuclear factor kappa-B (RANK), on osteoclast precursors and mature osteoclasts promotes the terminal differentiation, activation, and survival of osteoclasts, which in turn stimulate bone resorption. Denosumab targets the process of bone resorption by binding with a high degree of specificity and affinity to RANKL, preventing the activation of RANK and thus, the stimulation of osteoclasts (Sohn et al 2014). Due to its key role in osteoclast activation, RANKL is instrumental in facilitating osteoclast-induced bone resorption across a range of bone diseases.

1.1.2. TVB-009 and Postmenopausal Osteoporosis

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Osteoporosis causes more than 8.9 million fractures annually worldwide, of which more than 4.5 million occur in the Americas and Europe (World Health Organization [WHO] 2004). According to the WHO diagnostic classification, osteoporosis is defined by bone mineral density (BMD) at the hip or lumbar spine that is less than or equal to

[2] PROLIA is a registered trademark of Amgen, Inc.
[3] XGEVA is a registered trademark of Amgen, Inc.

2.5 standard deviations (SD)s below the mean BMD of a young-adult reference population (Cosman et al 2014).

Osteoporosis in postmenopausal women and elderly men has been linked to estrogen deficiency (Riggs 2000). Estrogen is critical for skeletal homeostasis and regulation of bone remodeling, in part, by modulating the expression of RANKL (Streicher et al 2017). Current Food and Drug Administration (FDA)-approved pharmacologic options for osteoporosis are bisphosphonates, calcitonin, estrogen agonist/antagonist, estrogens and/or hormone therapy, tissue-selective estrogen complex, parathyroid hormone 1-34, and RANK ligand inhibitor (denosumab) (Cosman et al 2014).

TVB-009 is intended in the US for the same indications as PROLIA US and TVB-009 is intended in Europe for the same indications as PROLIA EU. PROLIA is currently approved for treatment of postmenopausal women with osteoporosis at high risk for fracture; treatment to increase bone mass in men with osteoporosis; treatment of glucocorticoid-induced osteoporosis; treatment of bone loss in men receiving androgen-deprivation therapy for prostate cancer; treatment of bone loss in women receiving adjuvant-aromatase-inhibitor therapy for breast cancer (US only) (PROLIA United States Prescribing Information [USPI] 2020; PROLIA Summary of Product Characteristics [SPC] 2020).

1.1.3. Purpose of the Study

TVB-009 is a biosimilar candidate for PROLIA. The purpose of the study is to compare the efficacy, safety, and immunogenicity of TVB-009P and PROLIA US in patients with postmenopausal osteoporosis (PMO).

1.2. Findings from Nonclinical and Clinical Studies

1.2.1. Nonclinical Studies

Teva has addressed the nonclinical requirements in the development of TVB-009 as a biosimilar candidate to PROLIA in a single-dose comparative study with a 43-day follow-up period in cynomolgus monkeys, under Good Laboratory Practice (GLP). Results indicate similar safety characteristics, pharmacodynamics in terms of bone turnover biochemical markers, and exposure of the investigational medicinal products (IMP)s and support the safety of the planned clinical trials.

Further information can be found in the current version of the TVB-009 Investigator's Brochure (IB).

1.2.2. Clinical Studies

Clinical data for TVB-009P are available from a single study (Study TVB009-BE-10157). This first-in-human study was a randomized, double-blind, single-dose, parallel-group, 3-arm study to investigate the pharmacokinetic, pharmacodynamic, and safety similarity of 60 mg TVB-009P versus 60 mg denosumab (PROLIA US and PROLIA EU) in healthy subjects.

A total of 345 healthy subjects were enrolled into the study and randomly assigned to receive a single subcutaneous (sc) injection of

- 60 mg TVB-009P (115 subjects), or

- 60 mg PROLIA US (115 subjects), or
- 60 mg PROLIA EU (115 subjects)

The injections were administered on day 1 of the study via single-dose prefilled syringes after fasting (at least for 10 hours). Subjects were followed for up to 252 days (36 weeks).

1.2.2.1. Pharmacokinetics

Denosumab serum concentrations were measured in serum samples for up to 252 days after administration of TVB-009P, PROLIA US, or PROLIA EU using a validated assay. All 3 groups had a similar mean denosumab serum concentration-time profile. After reaching peak mean concentrations between approximately 1 and 2 weeks post-dose, denosumab was eliminated gradually in a multiphasic manner.

Pharmacokinetic similarity was demonstrated between TVB-009P and PROLIA US, TVB-009P and PROLIA EU, and PROLIA US and PROLIA EU: for each comparison the 90% confidence intervals (CI) for the geometric mean ratios (GMR) were fully contained within the pre-defined limits of 0.800 to 1.2500 for each of the 3 co-primary endpoints (maximum observed drug concentration [C_{max}], area under the concentration-time curve from time 0 to the time of the last measurable concentration [AUC_{0-t}], and area under the concentration-time curve from time 0 to infinity [AUC_{0-inf}]).

The evaluation of the secondary pharmacokinetic parameters (time to maximum observed drug concentration [t_{max}], percentage extrapolated area under the concentration-time curve [$\%AUC_{ext}$], apparent total body clearance [CL/F], apparent volume of distribution [V_z/F], terminal elimination rate constant [λ_z] and terminal elimination half-life [$t_{½}$]) and partial AUCs supports that the pharmacokinetics of the 3 treatments are similar.

A [redacted] was seen for all 3 groups. The 90% CI for the GMRs were fully contained within the pre-defined limits (see above); however, the exposure to denosumab was slightly higher for PROLIA EU than for PROLIA US and for TVB-009P.

1.2.2.2. Pharmacodynamics

Three markers of bone turnover were assessed in the study: serum C-telopeptide cross-link of type 1 collagen (sCTX-1), procollagen type 1 N-terminal propeptide (P1NP), and urinary N-telopeptide corrected for urine creatinine levels (uNTX/Cr). For each marker, all 3 treatment groups had a similar concentration-time profile over the course of the study.

The mean percent change of sCTX-1 from baseline at Day 169 was a key pharmacodynamic endpoint of the study. For all 3 comparisons (TVB-009P and PROLIA US, TVB-009P and PROLIA EU, and PROLIA US and PROLIA EU) the 95% CI of the difference in the sCTX-1 percent change from baseline at Day 169 was fully contained within the predefined margin of ± 20%, demonstrating pharmacodynamic similarity of all 3 treatment groups.

1.2.2.3. Safety and immunogenicity

There were no serious adverse events, deaths, protocol-defined adverse events of special interest (anaphylaxis), and no adverse events leading to study discontinuation.

A total of 106 subjects (31%) reported at least 1 treatment-emergent adverse event. The percentage of subjects who reported at least 1 adverse event was slightly lower in the TVB-009P group (27%) than in the PROLIA US (33%) and PROLIA EU (32%) groups.

There were no clinically meaningful differences observed between the treatment groups for adverse events, laboratory tests, vital signs, electrocardiograms, and physical examination findings.

Most subjects (>95%) did not report any injection site findings. The only finding reported for more than 1 subject was mild erythema (surface diameter of 5 mm to ≤50 mm) at 20 minutes post-dose (12 subjects [3%], 3-5 subjects at each treatment group) and 1 hour post-dose (3 subjects [<1%]). No induration, warmth, swelling, or injection site pain was reported.

A total of 3 subjects (<1%) had detectable antidrug antibodies (ADA) against denosumab. Two of these subjects (one in the PROLIA EU group, the other in the PROLIA US group) were ADA positive before and after study drug administration. Their ADA titers were low and did not increase after study drug administration. One subject in the PROLIA US group had an ADA response after study drug administration with a very low ADA titer at 2 time points (log_{10} titers of 1.6 and 1.5 for Day 15 and Day 29, respectively; the subject discontinued from the study after day 29).

Overall, the safety profile of TVB-009P was similar to the safety profiles of PROLIA US and PROLIA EU in the study. The safety profile after administration of a single dose of TVB-009P in healthy subjects was as expected based on the known safety profile of PROLIA.

Further information can be found in the current version of the TVB-009 IB.

1.3. Known and Potential Benefits and Risks to Patients

1.3.1. Known and Potential Benefits and Risks of the Test Investigational Medicinal Product(s)

TVB-009 is being developed as a biosimilar candidate to PROLIA and XGEVA. The safety profile of TVB-009 is expected to be similar to that of PROLIA (see Section 1.3.2).

To date, no new identified or potential risks were observed in TVB-009 nonclinical and clinical studies. Additional information is available in the IB.

1.3.2. Known and Potential Benefits and Risks of Reference Investigational Medicinal Product

The identified and potential risks of PROLIA include: hypocalcemia, osteonecrosis of the jaw, hypersensitivity reactions, atypical subtrochanteric and diaphyseal femoral fractures, fracture healing complications, serious infections, dermatologic adverse reactions, musculoskeletal pain, multiple vertebral fractures following discontinuation of treatment, suppression of bone turnover and reproductive toxicity (PROLIA USPI 2020).

Additional information regarding benefits and risks to patients may be found in the PROLIA EU SPC (2020).

1.3.3. Overall Benefit and Risk Assessment

TVB-009P is an intended biosimilar to PROLIA and physiochemical and functional characterization have shown similarity between the products.

In Study TVB009-BE-10157, TVB-009P [redacted] showed similar pharmacokinetics and similar pharmacodynamic effects on bone metabolism compared to both PROLIA sourced from the US and PROLIA sourced from the EU (see Section 1.2.2 for details). Comparison of the safety and immunogenicity between TVB-009P and PROLIA (US and EU) did not show any clinically relevant differences.

In patients with PMO the risk of fracture is high, and the patients are likely to derive significant benefit from a bone forming agent in clinical practice.

All patients in the study will receive active osteoporosis treatment for 18 months, either PROLIA US or TVB-009P or both, which is expected to show no relevant clinical difference in efficacy and safety compared to PROLIA.

The TVB-009P and PROLIA dosing schedule, ie, 60 mg administered as a single sc injection once every 6 months, reflects the recommendation for PROLIA to treat postmenopausal women with osteoporosis at high risk for fracture. Patients will be adequately supplemented with calcium and vitamin D.

The risks of treatment with TVB-009P are expected to be similar to the known risks of treatment with denosumab. Patients will be undergo safety monitoring and evaluation throughout the study as detailed in Section 7.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary and Secondary Study Objectives and Endpoints

The primary and secondary study objectives and endpoints are:

Objectives	Endpoints
The **primary objective** of the study is to demonstrate that there are no clinically meaningful differences in efficacy between TVB-009P and PROLIA US administered subcutaneously in patients with postmenopausal osteoporosis.	The primary efficacy endpoint is • the percent change from baseline in lumbar spine-bone mineral density (LS-BMD) at week 52 based on centrally assessed dual-energy X-ray absorptiometry (DXA) measurements • The co-primary efficacy endpoint for the European Union (EU) submission is the percent change from baseline in serum C-telopeptide cross-link of type 1 collagen (sCTX-1) at week 26. For the EU submission, this endpoint is regarded as co-primary. For the United States (US) submission, this endpoint is regarded as secondary
A **secondary objective** is to compare further efficacy and pharmacodynamic parameters between TVB-009P and PROLIA US.	The secondary efficacy and pharmacodynamic endpoints are: • percent change from baseline in LS-BMD at week 26 based on centrally assessed DXA measurements • percent change from baseline in femoral neck bone mineral density (BMD) by DXA at week 26 and at week 52 • percent change from baseline in total hip BMD by DXA at week 26 and at week 52 • percent change from baseline in sCTX-1 at all time points • sCTX-1 suppression at week 4 • percent change from baseline in procollagen type 1 N propeptide (P1NP) at week 26 and week 52 • incidence of fractures up to week 52
A **secondary objective** of the study is to compare efficacy and pharmacodynamic parameters between TVB-009P and PROLIA US after a single transition from PROLIA US to TVB-009P.	The pharmacodynamic/efficacy endpoints in the transition period are: • percent change from week 52 in LS-BMD by DXA at week 78 • difference between percent change from baseline in sCTX-1 between week 52 and week 78 • percent change from week 52 in femoral neck BMD by DXA at week 78 • percent change from week 52 in total hip BMD by DXA at week 78 • difference between percent change from baseline in P1NP between week 52 and week 78 • incidence of fractures up to week 78
A **secondary objective** of this study is to compare the safety and tolerability, including device-related events, between TVB-009P and PROLIA US throughout the study. A **secondary objective** of this study is to compare the safety and tolerability	The safety and tolerability endpoints are: • adverse events (and the number of patients who withdraw from the study due to adverse events) • vital signs • laboratory tests (hematology, serum chemistry, and urinalysis)

Objectives	Endpoints
between TVB-009P and PROLIA US after a single transition from PROLIA US to TVB-009P, including device-related events.	• electrocardiogram (ECG) • local tolerability at injection site • use of concomitant medications • device-related adverse events and malfunctions
A **secondary objective** of this study is to assess the immunogenicity of TVB-009P in comparison with PROLIA US throughout the study. A **secondary objective** of this study is to assess the immunogenicity of TVB-009P in comparison with PROLIA US after a single transition from PROLIA US to TVB-009P.	The immunogenicity endpoint is: • incidence of patients with confirmed positive anti-drug antibody (ADA) sample For confirmed positive samples, the ADA titer and the neutralizing potential will be tested. The effect of positive immunogenicity findings on pharmacokinetics, efficacy, and safety will be assessed if applicable.

Exploratory Objectives and Endpoints

Objectives	Endpoints
An **exploratory objective** of this study is to compare pharmacokinetics between TVB-009P and PROLIA US throughout the study.	The pharmacokinetic endpoints are: • serum concentration before next dose (C_{trough}), before second and third dose, and 6 months after third dose • serum concentration at 2 weeks postdose (C_{2weeks}) Pharmacokinetic endpoints derived from population pharmacokinetics analysis are: • area under the curve over the dosing period ($AUC_{0\text{-}tau}$) after first dose • C_{trough} before second dose • maximum observed concentration (C_{max}) after first dose

Primary Estimand: The primary estimand assesses clinically meaningful differences in effectiveness in patients with PMO, based on surrogate measures, focusing on the causal effects attributable to the IMP.

The primary estimand is the difference in mean percent change in lumbar spine-bone mineral density (LS-BMD) from baseline at week 52 between TVB-009P and PROLIA US treatment arms, regardless of intercurrent events in the target population of patients with PMO who receive at least one dose of IMP and have both a baseline and at least 1 post-baseline assessment of LS-BMD. For the submission in the US, this estimand is regarded as primary and for the submission in the European Union (EU), this estimand is regarded as co-primary.

The co-primary estimand for the EU filing is the difference in mean percent change in sCTX-1 from baseline at week 26, between TVB-009P and PROLIA US treatment arms, regardless of intercurrent events in the target population of patients with PMO. The same analysis set will be used for both estimands and therefore patients who terminate before week 26 will not be included in the sCTX-1 analysis. For the EU submission, this estimand is regarded as co-primary. For the US submission, this estimand is regarded as secondary.

2.1.1. Justification of Primary Endpoint

The primary endpoint of the study is the percent change in LS-BMD from baseline to week 52. This primary endpoint was agreed with FDA and European Medicines Agency (EMA) as being sensitive enough to confirm that there is no relevant clinical difference in efficacy between TVB-009P and PROLIA US. LS-BMD is a reliable, well-established, and reproducible measure of bone quality and fracture resistance, and is reasonably likely to predict beneficial response to treatment with anti-osteoporosis drugs. The treatment duration of 52 weeks for the evaluation of LS-BMD is expected to be long enough to be able to evaluate comparability of the 2 study medications.

The percent change from baseline in the biomarker sCTX-1 at week 26 is a co-primary endpoint for EU submission. In several clinical studies with denosumab it was demonstrated that sCTX-1 suppression is an indicator of denosumab effectiveness, as demonstrated by percent change from baseline (Wang et al 2009). Week 26 is regarded as the most appropriate time point for detecting difference in clinical efficacy, as for PROLIA, the difference across various drug doses in percent change in sCTX-1 is most evident at 6 months after start of treatment.

3. STUDY DESIGN

3.1. General Study Design and Study Schematic Diagram

This is a randomized, double-blind, multinational, multicenter study to demonstrate similar efficacy and safety of TVB-009P compared to PROLIA US administered in 3 sc doses of 60 mg every 26 weeks (3 injections) in patients with PMO. This study will consist of a screening period (up to 4 weeks) and a 52-week double-blind main treatment period, followed by a 26-week double-blind transition period.

The total duration of the study for each patient is approximately 82 weeks.

Screening will take place within 4 weeks before the first dose. After informed consent is obtained, eligibility criteria will be reviewed and screening evaluations will be performed.

At baseline, patients will be randomized in a 1:1 ratio to receive the first 2 doses of TVB-009P or PROLIA US (“main treatment period"). The first dose of TVB-009P or PROLIA US will be administered following randomization. The second dose will be administered 26 weeks after the first dose.

At week 52 (26 weeks after the second dose and prior to receiving their third dose), patients in the PROLIA US arm will be re-randomized 1:1 to either continue with a third dose of PROLIA US or transition to TVB-009P and receive a single dose of TVB-009P in the transition period to assess primarily immunogenicity and safety after a transition from PROLIA US to TVB-009P. All patients in the TVB-009P group will continue treatment with a third dose of TVB-009P. All patients who do not terminate the study before the third dose will be followed for 26 weeks after the third dose of study drug.

Final procedures and assessments will be performed at the end of study (EOS) visit at the end of the 78-week study period. Patients who withdraw from the study before completing the 78-week study period will have early termination (ET) procedures and assessments performed at their final visit. A patient who is randomized but does not complete all treatment periods will not be replaced. In case the assessment of LS-BMD is missing or not evaluable from more than 10% of the patients at the week 26 visit, the sponsor may decide to continue the recruitment of patients in order to increase the number of evaluable patients.

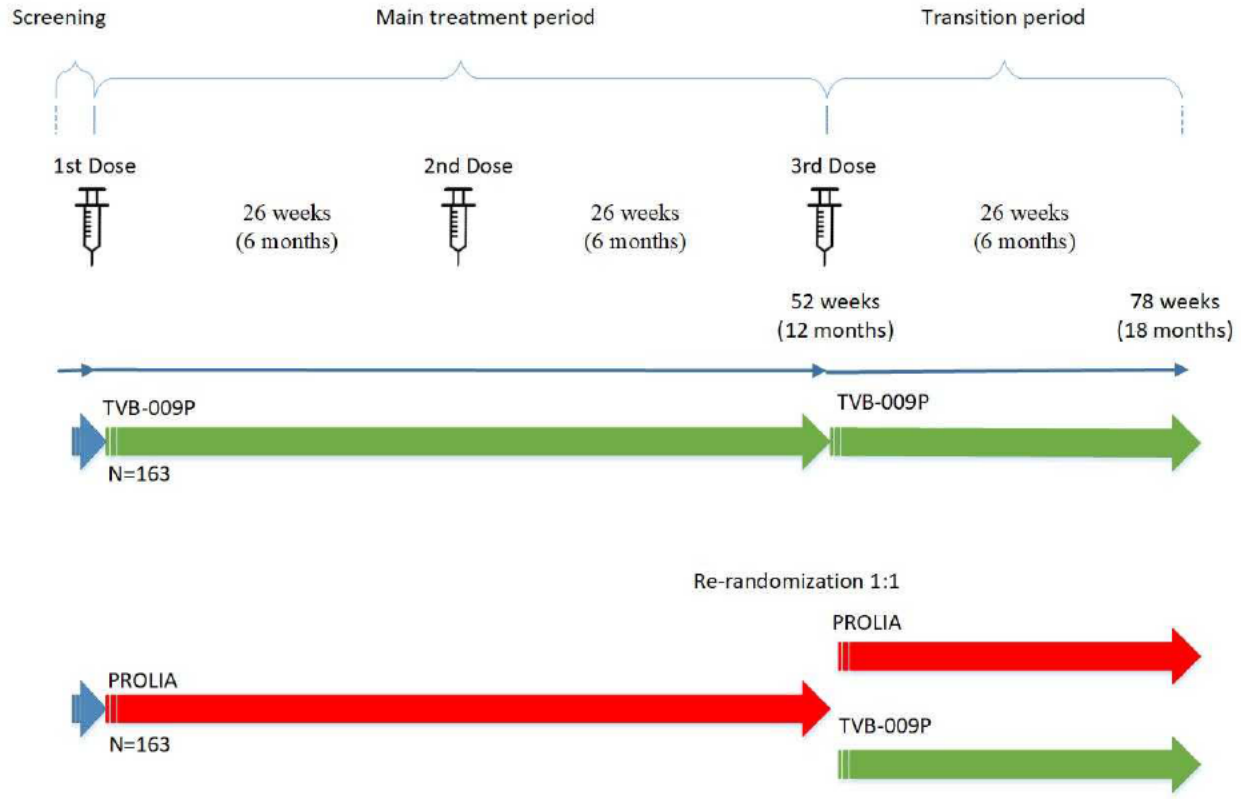
The EOS is defined as the last visit of the last patient of the transition period.

Details of study management during a COVID-19 outbreak are given in Appendix M.

The assessments and procedures performed during each study visit are detailed in Table 1 and Appendix B.

The study schematic diagram is presented in Figure 1.

Figure 1: Overall Study Schematic Diagram



N=number.

3.2. Planned Number of Patients and Countries

Approximately 326 patients (163 per arm) will be randomized to achieve approximately [redacted] at the end of the main 52-week treatment period.

Details on the definition of evaluable patients and sample size are given in Section 9.

The study is planned to be conducted in approximately 10 countries in approximately 75 investigational centers. [redacted]

3.3. Justification for Study Design and Selection of Population

The design of the current study in patients with PMO was agreed with the FDA and EMA and is regarded as appropriate to show that there is no clinically meaningful difference in efficacy, safety, and immunogenicity between TVB-009 and PROLIA. The study population as defined by the inclusion and exclusion criteria is a sensitive and homogenous population similar to the population of the clinical studies performed for the approval of PROLIA.

Patients in the PROLIA US arm will be re-randomized to either continue with PROLIA US or transition to TVB-009P to assess whether a single transition would result in an increased risk in terms of hypersensitivity, immunogenicity, or other reactions.

3.4. Stopping Rules for the Study

There are no formal rules for ET of this study. During the conduct of the study, serious adverse events will be reviewed (Section 7.1.5) as they are reported from the investigational centers to identify safety concerns.

The study may be terminated by the sponsor for any reason at any time. For example, the sponsor should terminate the study in the event of:

- new toxicological or pharmacological findings or safety issues that invalidate the earlier positive benefit-risk assessment
- discontinuation of the development of the IMP

If the whole study or arms of the study will be stopped, the patients who are terminated early will be followed according to Withdrawal Criteria and Procedures for the Patient (Section 4.3).

3.5. Schedule of Study Procedures and Assessments

Study procedures and assessments with their time points are presented in Table 1. Detailed descriptions of each method of procedures and assessments are provided in Section 6 (efficacy and pharmacodyamics assessments), Section 7 (safety assessments), and Section 8 (pharmacokinetics and immunogenicity assessments). Study procedures and assessments by visit are listed in Appendix B.

Table 1: Study Procedures and Assessments

Study period	**Screen-ing**	**Base-line**	**Main treatment period**								**Transition period**		
Visit number	**V1**	**V2**	**V3[a]**	**V4[a]**	**V5[a]**	**V6[a]**	**V7**	**V8[a]**	**V9[b]**		**V10[a]**	**V11[a]**	**V12**
									EOM	**SOT**			**EOS/ET**
Day/week and allowed time windows	**Up to 4 weeks before V2**	**Day 1**	**Day 15 ±3 days**	**Week 4 ±3 days**	**Week 8 ±5 days**	**Week 12 ±7 days**	**Week 26 ±7 days**	**Week 39 ±14 days**	**Week 52 ±14 days**		**Week 54 2 weeks ±3 days after V9**	**Week 65 13 weeks ±14 days after V9**	**Week 78 26 weeks ±14 days after V9**
Procedures and assessments													
Informed consent	X												
Inclusion and exclusion criteria	X	X											
Demographics/medical history	X												
Vitamin D and calcium dispensing[c]	X												
Pregnancy test (urine dipstick)		X[d]											
COVID-19 viral test[e]	X												
Randomization		X								X[f]			
IMP administration[g]		X[h]					X[h]			X[h]			
Prior medication and treatment history	X	X											
Local tolerability at the injection site		X[i]					X[i]			X[i]			
Clinical laboratory tests sampling (serum chemistry, hematology, and urinalysis)[j]	X[k l]	X		X		X[l]	X[l]	X	X[l]			X	X[l]
Immunogenicity		X[n]	X	X	X	X	X[n]	X	X[n]		X	X	X

Study period	**Screen-ing**	**Base-line**	**Main treatment period**								**Transition period**		
Visit number	**V1**	**V2**	**V3[a]**	**V4[a]**	**V5[a]**	**V6[a]**	**V7**	**V8[a]**	**V9[b]**		**V10[a]**	**V11[a]**	**V12**
									EOM	**SOT**			**EOS/ET**
Day/week and allowed time windows	**Up to 4 weeks before V2**	**Day 1**	**Day 15 ±3 days**	**Week 4 ±3 days**	**Week 8 ±5 days**	**Week 12 ±7 days**	**Week 26 ±7 days**	**Week 39 ±14 days**	**Week 52 ±14 days**		**Week 54 2 weeks ±3 days after V9**	**Week 65 13 weeks ±14 days after V9**	**Week 78 26 weeks ±14 days after V9**
Procedures and assessments													
sampling (serum ADA)[m]													
Physical examination, including height and weight[o]	X						X		X				X
12-lead ECG	X	X					X		X				X
Vital signs measurement[p]	X	X	X	X	X	X	X	X	X		X	X	X
LS-BMD by DXA	X						X		X				X[q]
Total hip and femoral neck BMD by DXA[r]	X						X		X				X[q]
Lateral spine X-ray	X								X				X[q]
Pharmacokinetics sampling (serum concentration of IMP)		X	X	X	X	X	X	X	X		X	X	X
Pharmacodynamics sampling (sCTX-1 and P1NP)[s]		X	X	X	X	X	X	X	X		X	X	X
Adverse events inquiry	X	X	X	X	X	X	X	X	X		X	X	X
Concomitant medication inquiry	X	X	X	X	X	X	X	X	X		X	X	X
COVID-19 inquiry	X	X	X	X	X	X	X	X	X		X	X	X

Study period	**Screen-ing**	**Base-line**	**Main treatment period**								**Transition period**		
Visit number	**V1**	**V2**	**V3[a]**	**V4[a]**	**V5[a]**	**V6[a]**	**V7**	**V8[a]**	**V9[b]**		**V10[a]**	**V11[a]**	**V12**
									EOM	**SOT**			**EOS/ET**
Day/week and allowed time windows	**Up to 4 weeks before V2**	**Day 1**	**Day 15 ±3 days**	**Week 4 ±3 days**	**Week 8 ±5 days**	**Week 12 ±7 days**	**Week 26 ±7 days**	**Week 39 ±14 days**	**Week 52 ±14 days**		**Week 54 2 weeks ±3 days after V9**	**Week 65 13 weeks ±14 days after V9**	**Week 78 26 weeks ±14 days after V9**
Procedures and assessments													
Inform of study restrictions and compliance requirements	X	X	X	X	X	X	X	X	X		X	X	

[a] Visits 3, 4, 5, 6, 8, 10, and 11 may be conducted at the patient's home should circumstances dictate.
[b] End of main treatment period is after all assessments (except for local tolerance at the injection site) have been performed at visit 9. Transition period begins with IMP administration.
[c] Vitamin D and calcium will be dispensed as necessary throughout the study to facilitate daily supplementation from screening to the end of the study.
[d] Prior to randomization.
[e] COVID-19 test can be performed at any time the patient displays symptoms of the disease.
[f] Patients in the PROLIA US treatment group will be re-randomized prior to receiving their third dose in a 1:1 ratio to receive an additional dose of PROLIA US or switch to TVB-009P and receive a single dose of TVB-009P in the transition period. Patients who were initially randomized to TVB-009P will continue to receive TVB-009P; however, to maintain blinding, the randomization process will be performed for all patients (although only patients in the PROLIA US arm will actually be re-randomized).
[g] All the assessments scheduled for visits 2, 7, and 9, with the exception of local tolerability, will need to be completed before IMP administration.
[h] All device-related adverse events, malfunctions etc will be recorded; their impact relative to the safety and tolerability of the IMP will be evaluated.
[i] Local tolerability at the injection site will be assessed 1 hour ±10 minutes after IMP administration.
[j] Coagulation (INR, PT and PPT), cholesterol (LDL, HDL, HDL/total), triglycerides and urinalysis will only be conducted at visits 2, 7, and 9. Blood sampling for lipid profile should be taken in the morning hours after overnight fasting. Samples should be collected consistently at the same time of the day for an individual patient at all visits. Vigorous exercise should be avoided the day prior to sampling
[k] Additional laboratory parameters, such as FSH and E2 (as applicable), estimated glomerular filtration rate (eGFR) (using the Modification of Diet in Renal Disease [MDRD] formula), will also be assessed at screening.
[l] Vitamin D levels will be assessed at screening and visits 6, 7, 9, 12, and ET/EOS. Vitamin D and/or calcium supplements will be provided. A patient with a screening adjusted calcium level outside the normal range or serum 25 (OH) vitamin D level ≤20 ng/mL may be rescreened once to re-evaluate calcium and vitamin D level post repletion.
[m] If any severe hypersensitivity reaction (eg, anaphylaxis), serious adverse or immunogenicity-related adverse event is observed, additional sample(s) will be collected for immunogenicity assessment as close to onset of the event as possible, at resolution of the event, and 30 days following the event onset, if possible.
[n] When a number of assessments are to be conducted at the same time point, the immunogenicity blood sample should be taken after other assessments but before IMP administration.
[o] Physical examination will include, at a minimum, head, eyes, ears, nose, and throat (HEENT), oral cavity, chest, cardiovascular system, abdomen, and skin. Oral examination will be performed to exclude risks for osteonecrosis of the jaw. If required by local authorities, a mandible radiograph may be carried out at screening.

[p] Vital signs includes pulse rate, blood pressure (systolic/diastolic), and respiratory rate. Before blood pressure and pulse are measured, the patient must rest in a supine or seated position for at least 5 minutes. The same position and arm should be used each time vital signs are measured for a given patient. For any abnormal vital signs value, the measurement should be repeated as soon as possible. In the event of suspected severe hypersensitivity (including anaphylaxis), vital signs, including oxygen saturation and respiration rate, will be measured.

[q] In case of early termination, LS-BMD DXA, total hip and femoral neck BMD DXA, and lateral spine X-ray will be assessed only in patients who terminate the study between the week 26 and week 52 visits. The minimum time between two DXA scans should be 3 months. These assessments will not be performed for patients who terminate the study earlier than week 26 or during the transition period.

[r] These scans will be unilateral only. For each patient, the same hip should be scanned throughout the study.

[s] Blood sampling for sCTX-1 and P1NP assessment should be taken in the morning hours after overnight fasting. Samples should be collected consistently at the same time of the day for an individual patient at all visits. Vigorous exercise should be avoided the day prior to sampling.

ADA=anti-drug antibody; BMD=bone mineral density; COVID-19=coronavirus 2019; DXA=dual-energy X-ray absorptiometry; ECG=electrocardiogram; E2=estradiol; EOM=end of main treatment period; EOS=end of study; ET=early termination; FSH=follicle stimulating hormone; HDL=high density lipoprotein; IMP=investigational medicinal product; INR=international normalized ratio; LDL=low density lipoprotein; LS-BMD=lumbar spine-bone mineral density; P1NP=procollagen type 1 N propeptide; PK=pharmacokinetic; PPT=partial prothrombin; PT=prothrombin; sCTX-1=serum C-telopeptide cross-link of type 1 collagen; SOT=start of transition period; V=visit.

4. SELECTION AND WITHDRAWAL OF PATIENTS

Prospective waivers (exceptions) from study inclusion and exclusion criteria to allow patients to be randomized/enrolled are not granted by Teva (Appendix C).

4.1. Patient Inclusion Criteria

Patients may be included in this study only if they meet all of the following criteria:

a. The patient provides a signed and dated written informed consent.

b. The patient is a clinically stable, ambulatory, female postmenopausal adult (≥60 and ≤90 years) with a diagnosis of osteoporosis.

c. The patient is of postmenopausal status, defined as:

- Spontaneous amenorrhea for >12 months, or
- Spontaneous amenorrhea >6 months and serum follicle stimulating hormone (FSH) and estradiol (E2) in menopausal range, or
- Surgical menopause at least 6 weeks before the start of screening.

d. The patient has a body weight ≥50 kg and ≤90 kg (≥110 lb and ≤198 lb) at screening.

e. The patient agrees to be supplemented with 1000 mg calcium and at least 400 IU vitamin D daily from screening until the last visit.

f. The patient has a BMD-measurement T-score of less than -2.5 but not less than -4.0 by dual energy X-ray absorptiometry (DXA) at the lumbar spine at screening based on central reader assessment.

g. The patient has at least three (3) vertebrae in the L1-L4 region that are evaluable by DXA.

h. The patient has serum 25 (OH) vitamin D level >20 ng/mL at screening and no current hyper- or hypocalcemia, defined as albumin-adjusted serum calcium outside the normal range, as assessed by the central laboratory. Vitamin D and calcium supplements will be provided and patients may be rescreened once to re-evaluate calcium and/or vitamin D level post repletion.

i. The patient must be willing and able to comply with study restrictions and to remain at the investigational center for the required duration during the study period, and willing to return to the investigational center for further visits, as applicable, and the follow-up procedures and assessments as specified in this protocol.

4.2. Patient Exclusion Criteria

Patients will be excluded from participating in this study if they meet any of the following criteria:

a. The patient has a known malabsorption of calcium or vitamin D supplements.

b. The patient has a metabolic or bone disease (except osteoporosis) such as Paget's disease, Cushing's disease, rheumatoid arthritis, sclerosteosis, osteomalacia, osteogenesis imperfecta, osteopetrosis, ankylosing spondylitis, hyperprolactinemia, malabsorption syndrome, osteomyelitis, multiple myeloma or related lymphoproliferative disorder, or bone metastases.

c. The patient has a current, uncontrolled hyperthyroidism or hypothyroidism, per patient report or chart review.

d. The patient has hypoparathyroidism or hyperparathyroidism (irrespective of current controlled or uncontrolled status).

e. The patient has a history and/or presence of risk factors of osteonecrosis of the jaw, as determined by the principal investigator, (eg, unhealed open soft tissue lesions in the mouth, poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, recent or planned invasive dental procedures such as tooth extractions within the next 18 months), presence of anemia or coagulopathy at screening, and/or inability to maintain oral hygiene during the study.

f. The patient has a history and/or presence of 1 severe or more than 2 moderate vertebral fractures (as determined by central reading of lateral spine X-ray during the screening period).

g. The patient has a history and/or presence of hip fracture or atypical femur fracture.

h. The patient has participated in another study of an IMP (or a medical device) within the previous 30 days or 5 half-lives of the IMP (whichever is longer) or longer if required by local regulations, or is currently participating in another study of an IMP (or a medical device).

i. The patient has a known hypersensitivity to any components of the IMPs stated in this protocol or to calcium or vitamin D.

j. The patient has a renal impairment manifested with an estimated glomerular filtration rate (eGFR) <45 mL/min.

k. The patient has cardiac disease as per investigator's discretion, including electrocardiogram (ECG) abnormalities at screening indicating significant risk of safety for patients participating in the study.

l. The patient has a malignancy or past malignancy (except for local non-melanoma skin cancer fully resected).

m. The patient has a current skin infection(s).

n. The patient has infectious disease:

   – Acute infection and/or antibiotic treatment must be resolved 28 days prior to the first dose of IMP.

   – Any relevant chronic infection.

   – Ongoing hepatitis B, hepatitis C, human immunodeficiency virus (HIV) Types 1 or 2 infection.

- Positive test for coronavirus disease 2019 (COVID-19) during screening or patient reporting a recent history of confirmed COVID-19 which had not fully recovered more than 14 days before screening.

o. The patient has any medical condition that (treated or untreated), in the opinion of the investigator, could jeopardize or would compromise the patient's safety or ability to participate in this study.

p. The patient has had any prior treatment with denosumab (PROLIA or XGEVA or biosimilars of denosumab products).

q. The patient has used intravenous bisphosphonates within less than 5 years prior to screening.

r. The patient has used oral bisphosphonates within the 12 months prior to start of screening and/or cumulative use >3 years before the start of screening.

s. The patient has ongoing use of any osteoporosis treatment (other than calcium and vitamin D supplements). The following rules for prior use of osteoporosis treatments have to be adhered to:

- Drugs being investigated for osteoporosis, eg romosozumab: dose received at any time.
- Strontium or fluoride (for osteoporosis): dose received at any time.
- Teriparatide or any parathyroid hormone (PTH) analogs: dose received within 12 months before the start of screening.
- Calcitonin: dose received within 6 months before the start of screening.
- Cinacalcet: dose received within 3 months before the start of screening.

t. The patient has ongoing use of any bone active drugs which can affect BMD including:

- Heparin (except topical), anti-convulsives (with the exception of benzodiazepines), systemic ketoconazole, adrenocorticotropic hormone, lithium, gonadotropin releasing hormone agonists, or anabolic steroids; dose received within 3 months before the start of screening.
- Systemic glucocorticosteroids: total cumulative dose of ≥50 mg within 3 months prior to randomization.
- Systemic oral or transdermal estrogen, or selective estrogen receptor modulators: more than 1 month of cumulative use within 6 months prior to randomization.

u. The patient is a pregnant or lactating woman, or plans to become pregnant during the study.

v. The patient has a history of chronic alcohol or drug abuse within the previous 6 months.

w. The patient is vulnerable (eg, people kept in detention).

4.3. Withdrawal Criteria and Procedures for the Patient

Each patient is free to withdraw from the study at any time, without prejudice to their continued care. Patients must be withdrawn from the study if any of the following events occur:

1. Patient withdraws consent or requests withdrawal from the study for any reason.
2. Patient is noncompliant with the study procedures and assessments in the opinion of the investigator.
3. The sponsor requests withdrawal of the patient.
4. Patient experiences an adverse event or other medical condition which indicates to the investigator that continued participation is not in the best interest of the patient, for example, but not limited to osteonecrosis of the jaw, atypical subtrochanteric and diaphyseal femoral fractures, serious infections, severe dermatologic adverse reactions or severe musculoskeletal pain.

Patients should be treated with standard of care and should be transitioned to another antiresorptive agent after withdrawal from or termination of the study as appropriate.

Investigators should attempt to obtain information on patients in the case of withdrawal from the study. Results of any evaluations and observations, together with a narrative describing the reason(s) for withdrawal from the study, must be recorded in the source documents. The case report form (CRF) must document the primary reason for withdrawal from the study.

If a patient experiences a BMD reduction of more than 7% from baseline at any time during the study, the investigator needs to discuss with the patient the implications for her fracture risk, alternative treatment options and the option for continuing in the study and to document that discussion and the decision made. If alternative treatment is recommended further study drug administration should be discontinued and every effort should be taken to complete remaining study visits in the main treatment period, regardless of the type of alternative treatment chosen by the subject.

If a patient exhibits clinical symptoms that may indicate COVID-19 infection after entering the study, the patient should be tested for active COVID-19 infection. If the patient tests positive for active COVID-19 infection, she may continue the study following the relevant local policies and study procedures including use of disallowed medications.

See Appendix E for information regarding how the study will define and address lost to follow-up patients to help limit the amount and impact of missing data.

If the reason for withdrawal from the study is an adverse event and/or clinically significant abnormal laboratory test result (with clinical significance meaning any variation in assessment results that has medical relevance and may result in an alteration in medical care [eg, active observation, diagnostic or therapeutic measures]), monitoring will be continued as applicable (eg, until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the test IMP/device or study procedure is made). The specific event or test result (including repeated test results, as applicable) must be recorded both on the source documentation and in the CRF; both the adverse events page and the relevant page of the CRF will be completed at that time.

The patient will be monitored as applicable (eg, until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the test IMP/device or study procedure is made). The investigator must inform the sponsor's medical expert as soon as possible of each patient who is being considered for withdrawal due to adverse events. Additional reports must be provided when requested.

If a patient is withdrawn from the study for multiple reasons that include also adverse events, the relevant page of the CRF should indicate that the withdrawal was related to an adverse event. An exception to this requirement will be the occurrence of an adverse event that in the opinion of the investigator is not severe enough to warrant discontinuation but that requires the use of a prohibited medication, thereby requiring discontinuation of the patient. In such a case, the reason for discontinuation would be "need to take a prohibited medication", not the adverse event.

In the case of patients lost to follow-up, attempts to contact the patient must be made and documented in the patient's medical records and transcribed to the CRF.

4.4. Replacement of Patients

A patient who is randomized but does not complete all treatment periods will not be replaced. In case the assessment of LS-BMD is missing or not evaluable from more than 10% of the patients at the week 26 visit, the sponsor might decide to continue the recruitment of patients in order to increase the number of evaluable patients.

4.5. Rescreening

A patient with a screening serum 25 hydroxy (OH) vitamin D level ≤20 ng/mL may be rescreened once to re-evaluate vitamin D level post repletion. Patients with albumin-adjusted serum calcium outside the normal range, as assessed by the central laboratory, may be rescreened once to re-evaluate calcium levels. Informed consent obtained at the beginning of the screening period also covers the partial rescreening for low vitamin D or for calcium; therefore reconsenting is not required.

4.6. Screening Failure

Screening failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study.

Selected information about patients who fail screening will be collected to comply with reporting and publishing requirements. This information may include, but is not limited to, demography, screening failure details, eligibility criteria, and any serious adverse events.

5. TREATMENTS

Investigational medicinal products are defined as the test IMP (TVB-009P) and reference IMP (PROLIA US). Patients will receive 3 injections of TVB-009P and/or PROLIA US at a dose of 60 mg, administered by a qualified healthcare provider (according to local regulations). Patients will also receive Vitamin D and calcium supplements (non-IMP).

5.1. Investigational Medicinal Products Used in the Study

5.1.1. Test Investigational Medicinal Product

TVB-009P is provided as a sterile, preservative-free, clear to opalescent, colorless to pale yellow aqueous solution for sc injection. It will be supplied in a combination product consisting of a pre-filled syringe (PFS) with an automatically activated needle safety guard for single-use administration. Each PFS of TVB-009P contains 60 mg TVB-009 in 1 mL of solution.

Patients will be administered TVB-009P as a single sc injection over >5 seconds in the abdomen (about 8 cm lateral from the umbilicus). Patients will be observed for a minimum of 1 hour after dosing. If the patient develops clinical symptoms, vital signs should be recorded and the patient should be assessed for anaphylaxis/hypersensitivity reactions as detailed in Appendix G.

Refer to Table 2 for specific details regarding TVB-009P. Additional details may be found in the pharmacy manual and in the Investigator's Brochure (IB) for TVB-009P.

5.1.2. Reference Investigational Medicinal Product

PROLIA US is supplied as a single dose PFS for sc injection with a manual needle guard. Each PFS of PROLIA contains 60 mg of denosumab in 1 mL of solution.

Patients will be administered PROLIA US as a single sc injection over >5 seconds in the abdomen (about 8 cm lateral from the umbilicus). Patients will be observed for a minimum of 1 hour after dosing. If the patient develops clinical symptoms, vital signs should be recorded and the patient should be assessed for anaphylaxis/hypersensitivity reactions as detailed in Appendix G.

Refer to Table 2 for specific details regarding PROLIA US. Additional details may be found in the pharmacy manual and in the PROLIA USPI.

Table 2: Investigational Medicinal Products Used in the Study

IMP name		**Test product**	**Reference product**
Trade name or company-assigned number		TVB-009P	PROLIA US
Formulation	Active	60 mg/mL	60 mg/mL
	Acetate	17 mM	17 mM
	Sorbitol	4.7%	4.7%
	Polysorbate 20	0.01%	0.01%
	Sodium hydroxide	pH to 5.2	pH to 5.2
	Water for injection	qs to 1 mL	qs to 1 mL
Unit dose strength(s)/Dosage level(s)		60 mg/mL 60 mg/dose	60 mg/mL 60 mg/dose
Route of administration		sc injection	sc injection
Device		Automatically activated needle safety guard	Manually activated needle safety guard
Manufacturer		Teva Branded Pharmaceutical Products R&D, Inc., West Chester, Pennsylvania, USA	Amgen Inc., One Amgen Center Drive, Thousand Oaks, California 91320-1799, USA
Storage conditions		2°C to 8°C (36°F to 46°F) and protected from direct light and heat. Avoid vigorous shaking	2°C to 8°C (36°F to 46°F) and protected from direct light and heat. Avoid vigorous shaking

IMP=investigational medicinal product; qs=quantum satis; sc=subcutaneous; USA=United States of America

5.1.3. Non-Investigational Medicinal Product Supplementation Treatment

Patients will be instructed to take 1000 mg calcium daily and at least 400 IU vitamin D daily from screening to week 78 (EOS). Calcium and vitamin D will be provided from local sources.

If hypocalcemia is detected, and there is no additional underlying reason, this should be further monitored and the below can be used for the corrective treatment:

- Mild to moderate hypocalcemia (≥ 7.5 mg/dL, < 8.4 mg/dL adjusted calcium): calcium, up to 3000 mg/day (oral) at the discretion of the investigator
- Symptomatic hypocalcemia or severe asymptomatic hypocalcemia (< 7.5 mg/dL adjusted calcium): intravenous calcium followed by oral calcium at the discretion of the investigator.

In case of continuous symptomatic or severe asymptomatic hypocalcemia the investigator should consider to postpone study drug administration by a maximum of 2 months and should discuss the situation with the medical monitor.

If hypercalcaemia is detected, supplementation with calcium and vitamin D should be interrupted and calcium levels should be further monitored; severe hypercalcaemia might be treated (eg, calcitonin or calcimimetics) at the discretion of the investigator. Patients will be allowed to continue treatment with study drug.

5.1.4. Medical Devices

The medical device for TVB-009P, manufactured by Teva and provided for use in this study is:

- PFS with an automatically activated needle safety guard for single-use administration

This automatically activated needle safety guard requires no additional actions by the user to shield the needle after use, and thus reduces the potential for accidental needle stick injuries.

The medical device for PROLIA US, manufactured by Amgen, Inc. and provided for use in this study is:

- PFS with manually activated needle safety guard for single-use administration

This manually activated needle safety guard requires the user to shield the needle after use.

Instructions for use of both devices are provided in the pharmacy manual.

All device-related adverse events, malfunctions etc. will be recorded; their impact relative to the safety and tolerability of the IMP will be evaluated (see Section 7.2 and Appendix H).

5.2. Preparation, Handling, Labeling, Storage, and Accountability for Investigational Medicinal Products

5.2.1. Storage and Security

The investigator or designee must confirm appropriate temperature conditions have been maintained for all IMPs received and any discrepancies are reported and resolved before use of the IMPs.

The IMPs (TVB-009P and PROLIA US) must be stored at a controlled temperature (2°C to 8°C [36°F to 46°F]) in a secure area (eg, locked refrigerator). The site should have a process for monitoring the storage temperature of unused IMP.

5.2.2. Labeling

Supplies of IMPs will be labeled according to the current ICH guidelines on GCP and Good Manufacturing Practice and will include any locally required statements. If necessary, labels will be translated into the local language.

5.2.3. Accountability

Each IMP shipment will include a packing slip listing the contents of the shipment, return instructions, and any applicable forms.

The investigator is responsible for ensuring that deliveries of IMPs and other study materials from the sponsor are correctly received, recorded, handled, and stored safely and properly in accordance with the CFR or national and local regulations, and used in accordance with this protocol.

Only patients screened and subsequently enrolled in the study may receive IMP/non-IMP and only authorized staff at the investigational center may supply IMP/non-IMP or administer IMP.

The pharmacist, designee or study drug administrator is responsible for IMP/non-IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final

disposition records). At the end of the study, a declaration will be signed stating that no unblinding of blinded study personnel occurred.

A record of IMP/non-IMP accountability (ie, IMP, vitamin D and calcium supplements, and other study materials received, used, retained, returned, or destroyed) must be prepared and signed by the pharmacist, designee or study drug administrator, with an account given for any discrepancies. Empty, partially used, and unused IMP/non-IMP will be disposed of or returned to Teva or its designee.

Further guidance and information are provided in the pharmacy manual.

5.3. Justification for Investigational Medicinal Products

5.3.1. Justification for Dose of Test Investigational Medicinal Product

The dose of IMP to be evaluated in this double-blind study (ie, 60 mg) was selected to match the approved dose for PROLIA.

5.3.2. Justification for Use of Reference Investigational Medicinal Product

TVB-009P is being developed as a potential biosimilar to the reference IMP, PROLIA. PROLIA US and PROLIA EU have been shown to be biosimilar in a previous pharmacokinetic/pharmacodynamic similarity study (see Section 1.2.2) – PROLIA US was selected as the reference IMP for this study.

5.4. Treatment After the End of the Study

After study end, no IMP will be provided as PROLIA is commercially available. Patients should be further treated with denosumab or should be transitioned to another antiresorptive agent as appropriate.

5.5. Restrictions

Patients will be required to comply with the following restrictions:

- Patients must remain seated, semi-recumbent, or supine as needed for assessments or other procedures, including dosing.
- Patients will fast overnight prior to the morning of blood sampling for sCTX-1 and P1NP assessment. Vigorous exercise should be avoided the day prior to sampling.
- Patients will fast overnight prior to the morning of blood sampling for lipid profiling.

There are no other restrictions in this study.

5.6. Prior and Concomitant Medication or Therapy

See Section 4.1 for patient inclusion and Section 4.2 patient exclusion criteria.

Any prior or concomitant therapy, medication (including prior osteoporosis medication), or procedure a patient has had from 4 weeks before screening through the end of the study will be recorded in the source documentation and in the CRF. Trade name and international nonproprietary name (INN) (if available), indication, dose, and start and end dates of the

administered medication or treatment will be recorded. The sponsor will encode all therapy and medication according to the World Health Organization Drug Dictionary (WHODrug Global).

Prohibited and restricted medications are listed in Appendix F.

At each visit at the investigational center after the screening visit the investigator will ask patients whether they have taken any medications, including over-the-counter medications, vitamins, or herbal or nutritional supplements, since the previous visit.

Concomitant medication and treatment will be recorded until the ET/EOS visit.

5.7. Procedures for Monitoring Patient Compliance

The investigator will be responsible for monitoring patient compliance with this protocol from the start of the screening period through the transition period. If the investigator or the sponsor determines that the patient is not in compliance with the study protocol, the investigator and the sponsor should determine whether the patient should be withdrawn from the study. The Independent Ethics Committee (IEC)/Institutional Review Board (IRB) should be notified if required by local regulation.

5.8. Randomization and Blinding

This is a randomized, double-blind study. Patients and investigators will remain blinded to IMP assignment during the study.

At baseline, patients will be randomized in a 1:1 ratio to receive the first 2 doses of TVB-009P or PROLIA US (“main treatment period”). The randomization will be stratified by region (US/non-US) and any use of previous bisphosphonates (yes/no). At week 52, prior to receiving their third dose of study medication, patients in the PROLIA US treatment group will be re-randomized in a 1:1 ratio to receive a third dose of PROLIA US or switch to TVB-009P (“transition period”) to receive a single dose of TVB-009P. The re-randomization will be stratified by region (US/non-US) and any use of previous bisphosphonates (yes/no). All patients in the TVB-009P group will receive a third dose of TVB-009P at week 52.

During the main treatment period, the sponsor, investigators (and other site staff involved in study assessments) and patients will be blinded to the treatment assignment of all patients. To maintain blinding of the patients and investigators (and other site staff involved in study assessments) to the treatment assignment of all patients during the entire study, and maintain blinding of the sponsor until the main treatment period is unblinded, the re-randomization process will be performed for all patients, including the patients in the TVB-009P group (although only patients in the PROLIA US group will actually be re-randomized while patients in the TVB-009P group will continue to receive TVB-009P in the transition period). The randomization will be implemented using Randomization and Trial Supply Management (RTSM).

At the investigational center, only the pharmacist or designee who will dispense the study drug and the study drug administrator will be unblinded. These staff will not participate in any efficacy, pharmacokinetic, pharmacodynamic, immunogenicity, and safety assessments.

5.9. Maintenance of Randomization and Blinding

5.9.1. Maintenance of Randomization

Patient randomization codes will be maintained in a secure location at the service provider contracted to generate the codes. At the time of final analyses, after receiving unblinding request from Teva statistician, the service provider will provide the unblinded IMP assignment according to the processes defined in the relevant Standard Operating Procedure (SOP).

5.9.2. Blinding and Unblinding

The study drug will be prepared in a separate room by the non-blinded pharmacist or designee. The pharmacist or designee will place the respective original box into a neutral container that is suitable to maintain the blind. The original study drug box and syringe will not be visible when the patient or any other blinded study team member enters the room since study drug packaging and the syringes differ among products. In order to ensure additional patient blinding, a blindfold with an additional pillow at chest level (or similar device) will be used during the study drug injection to shield the study drug from the patient. The investigator doing the safety assessment will remain blinded to treatment assignment.

Staff responsible for pharmacokinetic and immunogenicity bioanalysis, population pharmacokinetics, and/or pharmacokinetics/pharmacodynamics model will not have access to the patient treatment randomization prior to unblinding the study.

During the transition period, the sponsor, investigators (and other site staff involved in study assessments) and patients will be blinded to the randomized treatment of patients who received PROLIA US in the main treatment period and are re-randomized for the transition period.

Before database lock (DBL), staff responsible for efficacy and safety analysis, pharmacokinetic and immunogenicity bioanalysis, population pharmacokinetic analysis, and/or pharmacokinetic/pharmacodynamic analysis will not have access to the patient treatment randomization. After last patient last visit and DBL of the main treatment period, the sponsor will unblind the treatments for the analysis of the main treatment period (up to and including week 52; not including third IMP dose and assessments following the third dose). A full CSR will be prepared with all data related to the first and second doses up to the week 52 end of main treatment phase procedures.

Only after completion of the study (after week 78) and DBL will the transition period be fully unblinded and analyzed. The results will be reported separately in a CSR addendum, including any updates to the safety analysis of the main treatment period.

In case of an emergency, serious adverse event (see Section 7.1.5), or in cases when knowledge of the IMP assignment is needed to make treatment decisions, the investigator may unblind the patient’s IMP assignment as deemed necessary, mainly in emergency situations. Individual randomization codes, indicating the IMP assignment for each randomized patient, will be available to the investigator(s) or pharmacist(s) at the investigational center via the RTSM, both via telephone and internet. Breaking of the treatment code can always be performed by the investigator without prior approval by the sponsor; however, the sponsor should be notified following the breaking of the treatment code. The patient's assignment should not be revealed to the sponsor.

When a blind is broken for safety reasons, the patient will be withdrawn from the study and the event will be recorded on the CRF. The circumstances leading to the breaking of the code should be fully documented in the investigator's study files and in the patient's source documentation. Assignment of IMP should not be recorded in any study documents or source document.

In blinded studies, for an adverse event defined as a suspected unexpected serious adverse reaction (SUSAR) (ie, reasonable possibility; see Section 7.1.4), Global Patient Safety and Pharmacovigilance (GPSP) may independently request that the blind code be broken (on a case-by-case basis) to comply with regulatory requirements. The report will be provided in an unblinded manner for regulatory submission. If this occurs, blinding will be maintained for the investigator and for other personnel involved in the conduct of the study, and analysis and reporting of the data.

5.9.3. Data Monitoring Committee

There will be no Data Monitoring Committee in this study.

5.10. Total Blood Volume

The total blood volume to be collected for each patient in this study is approximately 250 mL.

Details on blood volumes to be collected during the study are provided in the informed consent form (ICF) and laboratory manual.

6. ASSESSMENT OF EFFICACY AND PHARMACODYNAMICS

6.1. Assessments of Efficacy

Refer to Table 1 for the timing of assessments and procedures. See Appendix B for a detailed description of assessments and procedures.

For screening purposes, X-rays or DXA scans taken up to 30 days prior to the beginning of the screening period may be used if all of the following criteria are met:

- Images are to be obtained in a manner consistent with the technique specified by the central imaging vendor for this study (refer to the appropriate imaging manuals provided) and are deemed useable by the central imaging vendor
- DXA images are to be obtained using the same DXA scanner that will be used for this study

6.1.1. Lumbar Spine-Bone Mineral Density by Dual-Energy X-Ray Absorptiometry

LS-BMD will be measured by DXA. Hologic and GE Lunar DXA machines will be used and the same machine should be used for all study procedures for a particular patient for the duration of the study. DXA machine changes during the study are strongly discouraged; however, if a machine is changed during the study, the central imaging vendor will oversee the change in order to minimize the impact on assessments of BMD change. All LS-BMD DXA scans will be submitted to and analyzed by the central imaging vendor. The results of the DXA scans after start of treatment will be provided to the investigator after completion of the study (after week 78) and DBL upon request of the patient and/or due to country regulation.

Lumbar spine scans must include L1 through L4. The vertebrae on which the measurement is based should be consistent throughout the study on an individual patient level.

A separate procedure manual provided by the central imaging vendor will detail the DXA machine types including specific instructions for acquisition of scans as well as performance of Instrument Quality Control.

6.1.2. Total Hip and Femoral Neck Bone Mineral Density by Dual-Energy X-Ray Absorptiometry

Total hip and femoral neck BMD will be measured by DXA. These scans will be unilateral only. For each patient, the same hip should be scanned throughout the study. Hologic and GE Lunar DXA machines will be used and the same machine must be used for all study procedures for a particular patient for the duration of the study. All hip and femoral neck bone DXA scans will be submitted to and analyzed by the central imaging vendor. Detailed instructions for scan acquisition can be found in the separate manual provided by the central imaging vendor. The results of the DXA scans after start of treatment will be provided to the investigator after completion of the study (after week 78) and DBL upon request of the patient and/or due to country regulation.

6.1.3. Lateral Spine X-Ray Vertebral Fracture Assessment

Patients will undergo a lateral spine X-ray for assessment of vertebral fractures by the central imaging vendor. Nominally, vertebral fracture will be assessed in all vertebrae from the fourth thoracic vertebra (T4) to the fourth lumbar vertebra (L4). Any new fracture should be reported as an adverse event (Section 7.1.2).

6.1.4. Assessment of Nonvertebral Fractures

Information about any nonvertebral fractures and level of trauma causing the fracture during the study will be recorded in the CRF. A copy of radiographs or other diagnostic confirming the fracture and/or a copy of the report should be included in the patient's study records. Additionally, any new fracture should be reported as an adverse event (Section 7.1.2).

6.2. Pharmacodynamics Assessment

Blood samples (4 mL) for assessment of sCTX-1 and P1NP will be collected via venipuncture or indwelling catheter before and up to 78 weeks after administration of first IMP dose at the time points detailed in Table 1. Blood sampling for sCTX-1 and P1NP assessment should be taken in the morning hours after overnight fasting. Samples should be collected consistently at the same time of the day for an individual patient at all visits (see Appendix I). Vigorous exercise should be avoided the day prior to sampling.

7. ASSESSMENT OF SAFETY

In this study, safety will be assessed by qualified study personnel by evaluating reported adverse events, local tolerability at the injection site, clinical laboratory test results, vital sign measurements, ECG findings, physical examination, and use of concomitant medication. Refer to Table 1 for the timing of assessments and procedures.

All assessments scheduled for baseline (day 1), week 26 and week 52 visits, with the exception of local tolerability, will be completed before IMP administration on those days.

Adverse events are categorized by ICH guidelines and adverse device effects are categorized and classified according to International Organization for Standardization (ISO) standard 14155:2011(E).

Device deficiencies that are not associated with an adverse event as well as those that have the potential to cause a serious adverse event are covered in Appendix H.

7.1. Adverse Events

7.1.1. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

In this study, any adverse event occurring after the patient has signed the ICF through the end of the study should be recorded and reported as an adverse event.

An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study. Development of a new condition or the worsening of a pre-existing condition will be considered an adverse event, whether or not considered related to TVB-009P. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during this study will not be considered adverse events.

Accordingly, an adverse event can include any of the following:

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication (including study provided medications)
- significant worsening (change in nature, severity, or frequency) of pre-existing conditions
  (Note: A condition recorded as pre-existing that is intermittently symptomatic [eg, headache] and that occurs during this study should be recorded as an adverse event)
- drug interactions

- events occurring during diagnostic procedures or during any washout phase of this study
- laboratory or diagnostic test abnormalities that result in the withdrawal of the patient from the study, are associated with clinical signs and symptoms or a serious adverse event, require medical treatment or further diagnostic work-up, or are considered by the investigator to be clinically significant. Note: Abnormal laboratory test results at the screening visit that preclude a patient from entering the study or receiving study treatment are not considered adverse events.

7.1.2. Recording and Reporting of Adverse Events

For recording of adverse events, the study period is defined for each patient as the time period from signature of the ICF to the end of the study. The period for reporting treatment-emergent adverse events is defined as the period after the first dose of IMP is administered until the end of the study.

All adverse events that occur during the defined study period must be recorded both on the source documentation and the CRF, regardless of the severity of the event or judged relationship to the IMP. For serious adverse events, the serious adverse event form must be completed and the serious adverse event should be reported within 24 hours of when the investigator becomes aware of the serious adverse event (Section 7.1.5.3.1). The investigator does not need to actively monitor patients for adverse events after the study period defined above.

At each contact with the patient, the investigator or designee must question the patient about adverse events by asking an open-ended question such as “Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe.” A precise diagnosis should be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively as a single diagnosis on the CRF and, if it is a serious adverse event, on the serious adverse event form. Reported or observed signs and symptoms that are not manifestations of a known diagnosis should be reported individually.

The clinical course of each adverse event will be monitored at suitable intervals until resolved, stabilized, or returned to baseline; or until the patient is referred for continued care to a health care professional; or until determination of a cause unrelated to the IMP or study procedure is made.

The onset and end dates, duration (in case of adverse event duration of less than 24 hours), action taken regarding IMP, treatment administered, and outcome for each adverse event must be recorded both on the source documentation and the CRF.

The relationship of each adverse event to the IMP, and the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described below.

7.1.3. Severity of an Adverse Event

The severity of each adverse event must be recorded as 1 of the following:

Mild: No limitation of usual activities

Moderate: Some limitation of usual activities

Severe: Inability to carry out usual activities

7.1.4. Relationship of an Adverse Event to the Investigational Medicinal Product

The relationship of an adverse event to the IMP will be made according to the criteria in Table 3.

Table 3: The Relationship of an Adverse Event to the Investigational Medicinal Product

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events that, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to adverse events that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the IMP.	The relationship of an adverse event may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if at least 2 of the following apply: • It does not follow a reasonable temporal sequence from the administration of the IMP. • It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It does not follow a known pattern of response to the IMP. • It does not reappear or worsen when the IMP is re-administered.
Reasonable possibility (related)	This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the administration of IMP cannot be ruled out with certainty.	The relationship of an adverse event may be considered "reasonable possibility" if at least 2 of the following apply: • It follows a reasonable temporal sequence from administration of the IMP. • It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear after discontinuation of the IMP, yet an IMP relationship clearly exists. • It follows a known pattern of response to the IMP.

IMP=investigational medicinal product.

7.1.5. Serious Adverse Events

For recording of serious adverse events, the study period is defined for each patient as the time period from signature of the ICF to the end of the study. Serious adverse events occurring in a patient after the end of the study should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1.

Further details are given in the Safety Monitoring Plan.

7.1.5.1. Definition of a Serious Adverse Event

A serious adverse event is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- results in death
- is life-threatening adverse event (ie, the patient was at risk of death at the time of the event); it does not refer to an event which hypothetically might have caused death if it were more severe
- requires inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event

  Hospitalizations scheduled before the patient signed the ICF will not be considered serious adverse events, unless there was worsening of the preexisting condition during the patient's participation in this study.

  Likewise, hospitalizations for a social reason only (eg, the subject lives far away and is allowed therefore to stay in the hospital overnight) will not be considered a serious adverse event.
- results in persistent or significant disability/incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- is a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.
- All occurrences of possible drug-induced liver injury that meet Hy's law criteria, defined as **all** of the below, must be reported by the investigator to the sponsor as a serious adverse event:
  - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increase of >3 × the upper limit of normal (ULN)
  - total bilirubin increase of >2 × ULN
  - absence of initial findings of cholestasis (ie, no substantial increase of alkaline phosphatase [ALP])

An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious adverse event.

7.1.5.2. Expectedness

In this study, the reference safety information (RSI) for TVB-009P for determination of a suspected serious adverse reaction is included in the IB. A serious adverse event that is not included in the relevant RSI by its specificity, severity, outcome, or frequency is considered an unexpected adverse event.

The RSI of PROLIA US in this study is the PROLIA USPI.

The sponsor's GPSP will determine the expectedness for all serious adverse events.

For the purpose of SUSAR reporting: if the patient is receiving TVB-009P, the version of the IB at the time of occurrence of the SUSAR will apply. If the patient is receiving PROLIA US, the PROLIA USPI effective at the time of the SUSAR occurrence will apply.

7.1.5.3. Reporting a Serious Adverse Event

7.1.5.3.1. Investigator Responsibility

To satisfy regulatory requirements, all serious adverse events that occur during the study, regardless of judged relationship to administration of the IMP, must be reported to the sponsor by the investigator. The event must be reported within 24 hours of when the investigator learns about it. Completing the serious adverse event form and reporting the event must not be delayed, even if not all the information is available. The investigator does not need to actively monitor patients for adverse events once this study has ended.

Serious adverse events occurring to the patient after the end of the study (or early termination, whichever applies) for that patient should be reported to the sponsor if the investigator becomes aware of them.

The serious adverse event form should be sent to the local safety officer (LSO) or designee (a Contract Research Organization [CRO] in a country without a sponsor LSO) (contact information is in the Clinical Study Personnel Contact Information section); the LSO will forward the report to the sponsor's GPSP.

In addition to the serious adverse event term, the following information should be provided to record the event accurately and completely:

- study number
- investigator and investigational center identification
- patient number
- onset date and detailed description of adverse event
- investigator's assessment of the relationship of the adverse event to the IMP (no reasonable possibility, reasonable possibility, as described in Table 3)

Additional information includes:

- age and sex of patient
- date of first dose of IMP
- date and amount of last administered dose of IMP
- action taken
- outcome, if known
- severity

- explanation of assessment of relatedness
- concomitant medication (including study provided medications; dates, doses, routes of administration, doses and dosing regimens)
- treatment for the event (in the narrative section)
- pertinent laboratory or other diagnostic test data
- medical history
- results of dechallenge/rechallenge, if known
- for an adverse event resulting in death
  - cause of death (whether or not the death was related to IMP)
  - autopsy findings (if available)

Each report of a serious adverse event will be reviewed and evaluated by the investigator and the sponsor to assess the nature of the event and the relationship of the event to the IMP.

In addition, the investigator will assess whether the etiology of the event is associated with the patient's primary condition, concomitant study medications (including study provided medications), study procedures, or underlying disease or any other condition.

Additional information (follow-up) about any serious adverse event unavailable at the initial reporting should be forwarded by the investigator within 24 hours of when it becomes known to the same address as the initial report.

For all countries, the sponsor's GPSP will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/Extensible Markup Language (XML) file or MedWatch of serious adverse events to the LSO/CRO for submission to the competent authorities, IEC/IRBs, and investigators, according to local regulations. The investigator must ensure that the IEC/IRB is also informed of the event, in accordance with national and local regulations.

The sponsor's GPSP will submit the XML of SUSARs to the EMA in an unblinded manner, when applicable and according to local regulations. Submission of SUSARs to the FDA using MedWatch forms is done in an unblinded manner by the Regulatory Affairs department upon receipt from the LSO.

For SUSARs occurring during the treatment period, only the LSO/unblinded personnel from the CRO will receive the unblinded report for regulatory submission; the others will receive a blinded report. If SUSARs occur after the treatment period, the sponsor will also receive an unblinded copy of the report.

7.1.5.3.2. Sponsor Responsibility

If a serious unexpected adverse event is believed to be related to the IMP or study procedures, the sponsor will take appropriate steps to notify all investigators participating in sponsored clinical studies of TVB-009P and the appropriate competent authorities (and IEC/IRB, as appropriate).

In addition to notifying the investigators and competent authorities (and IEC/IRB, as appropriate), other action may be required, including the following:

- altering existing research by modifying the protocol
- discontinuing or suspending the study
- modifying the existing consent form and informing all study participants of new findings
- modifying listings of expected toxicities to include adverse events newly identified as related to TVB-009P

7.1.6. Protocol-Defined Adverse Events of Special Interest

No protocol-defined adverse events of special interest are identified for this study.

7.1.7. Protocol Deviations Because of an Adverse Event

If a patient experiences an adverse event or medical emergency, deviations from the protocol may be allowed on a case-by-case basis. To ensure patient safety, after the event has stabilized or treatment has been administered (or both), the investigator or other physician in attendance must contact the CRO medical monitor as soon as possible to discuss the situation. The investigator, in consultation with the sponsor, will decide whether the patient should continue to participate in the study.

7.2. Adverse Device Effects

An adverse device effect is an adverse event related to the use of an investigational medical device or a combination product. This includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation, or any malfunction of the investigational medical device, including any event resulting from user error or from intentional misuse of the investigational medical device.

7.2.1. Adverse Device Effect Reporting

Adverse device effects (Figure 2) must be recorded both on the source documentation and the CRF.

All adverse device effects shall be reviewed by the investigator, the medical monitor, and the sponsor. The investigator and sponsor will record all relevant information regarding every adverse device effect/serious adverse device effect and will categorize each as guided in Section 7.2.2.1.

The investigator should make an initial determination if the adverse event may be related to a device deficiency.

Adverse device effects and device deficiencies will be listed in the CSR.

7.2.2. Serious Adverse Device Effects

A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event (Section 7.1.5.1).

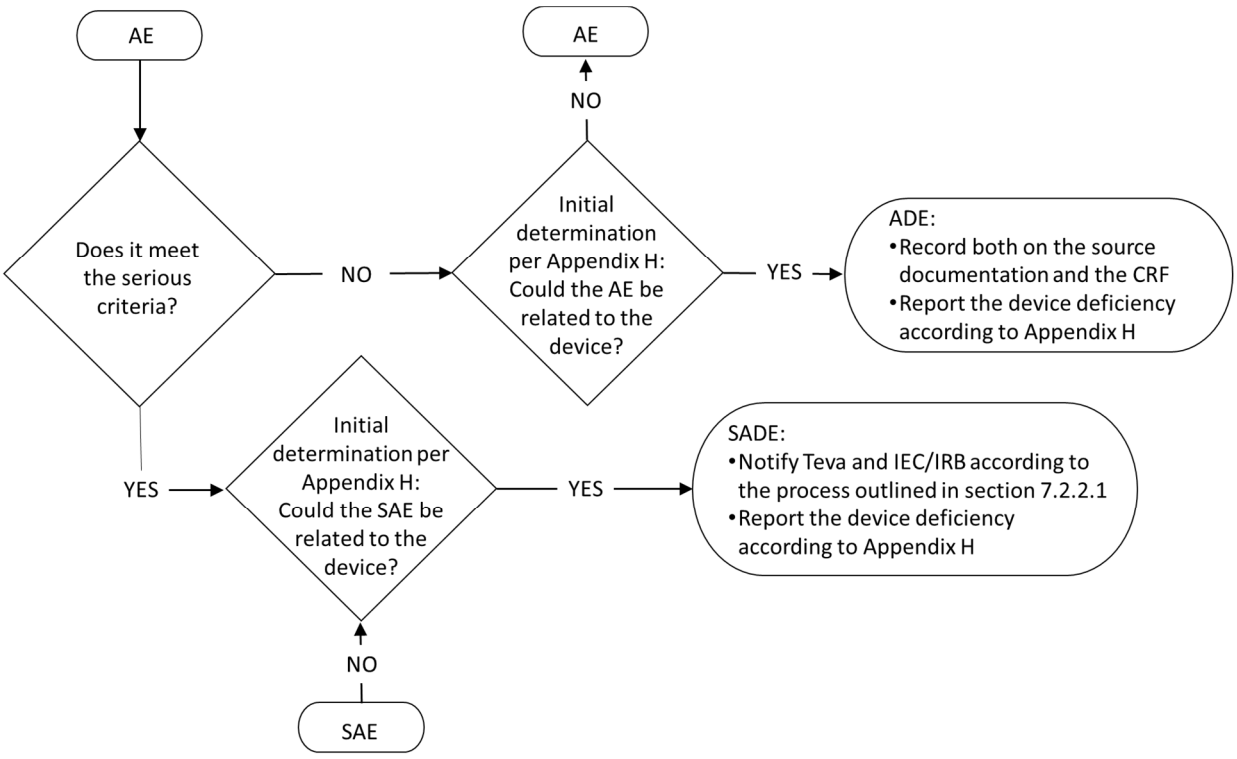
7.2.2.1. Serious Adverse Device Effect Reporting

The investigator will report to the sponsor, without unjustified delay, all serious adverse device effects (within 24 hours); this information shall be promptly followed by detailed written reports as described below.

The process and contact details for serious adverse device effect reporting are the same as for serious adverse event reporting provided in Section 7.1.5.3.

Events shall be reported to the IEC/IRB by the investigator and to the regulatory authorities by the sponsor using the appropriate form according to the national and local regulations.

Figure 2: Decision Tree for Adverse Events and Adverse Device Effects Classification



AE=adverse event; ADE=adverse device effect; CRF=case report form; IEC=Institutional ethics committee; IRB=Institutional Review Board; SADE=serious adverse device effect; SAE=serious adverse event.

7.3. Clinical Laboratory Tests

All clinical laboratory test results outside of the reference range will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

A laboratory test result that is judged by the investigator as clinically significant will be recorded both on the source documentation and the CRF as an adverse event, and monitored as described in Section 7.1.2.

Details of clinical laboratory tests are listed in Section 7.3.1 and will be referenced in the study laboratory manual.

7.3.1. Serum Chemistry, Hematology, and Urinalysis

Clinical laboratory tests (serum chemistry, hematology, and urinalysis) will be performed at the time points detailed in Table 1. Clinical laboratory tests will be performed using the central laboratory (see Appendix A). Specific laboratory tests to be performed are listed in Table 4.

Table 4: Clinical Laboratory Tests

Serum chemistry	Hematology	Urinalysis

• calcium
• phosphate
• sodium
• magnesium
• potassium
• chloride
• bicarbonate or carbon dioxide
• glucose
• blood urea nitrogen (BUN)
• creatinine
• estimated glomerular filtration rate (eGFR) (using the Modification of Diet in Renal Disease [MDRD] formula)
• total cholesterol (low density lipoprotein [LDL] and high density lipoprotein [HDL] HDL)
• triglycerides (after overnight fasting)
• uric acid
• alanine aminotransferase (ALT)
• aspartate aminotransferase (AST)
• lactic dehydrogenase (LDH)
• gamma glutamyl transpeptidase (GGT)
• alkaline phosphatase (ALP)
• creatine phosphokinase (CPK)
• total protein
• albumin
• total bilirubin
• vitamin D
	• hemoglobin
	• hematocrit
	• red blood cell (RBC) count
	• RBC indices
	• platelet count
	• absolute neutrophil count (ANC)
	• white blood cell (WBC) count and differential count
	  ○ polymorphonuclear leukocytes (neutrophils)
	  ○ lymphocytes
	  ○ eosinophils
	  ○ monocytes
	  ○ basophils
	• coagulation tests
	  ○ international normalized ratio (INR)
	  ○ prothrombin (PT)
	  ○ partial prothrombin (PTT)
		• protein
		• glucose
		• ketones
		• blood (hemoglobin)
		• ph
		• nitrates
		• specific gravity
		• microscopic
		  ○ bacteria
		  ○ RBCs
		  ○ WBCs
		  ○ casts
		  ○ crystals

7.3.2. Other Clinical Laboratory Tests

7.3.2.1. Follicle Stimulating Hormone

At screening, women will have a serum FSH assessment, as applicable, to confirm postmenopausal status.

7.3.2.2. Estradiol

At screening, women will have a serum E2 assessment, as applicable, to confirm postmenopausal status.

7.3.2.3. Urine Pregnancy Test

At day 1 (prior to randomization), a pregnancy test (urine dipstick) will be done to confirm that women are not pregnant.

7.3.2.4. Vitamin D

At screening, and at visits 6, 7, 9, 12, and EOS women will have a serum 25 (OH) vitamin D assessment.

7.3.2.5. Coronavirus Disease 2019 Testing

COVID-19 testing will be performed at screening. In addition, if a patient exhibits clinical symptoms after entering the study that may indicate infection, the patient should be tested for COVID-19.

COVID-19 testing will be performed locally (if available), or centrally (if not available locally) and reported in the CRF.

7.4. Physical Examinations

Physical examinations (will include, as a minimum, height in centimeters and weight in kilograms, and examination of head, eyes, ears, nose, and throat [HEENT], oral cavity, chest, cardiovascular system, abdomen, and skin) will be performed at the time points detailed in Table 1. Oral examination will be performed to exclude risks for osteonecrosis of the jaw. If required by local authorities, a mandible radiograph may be carried out at screening.

Any physical examination finding that is judged by the investigator as clinically significant (except at the initial screening visit, which will be captured as medical history) will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2.

7.5. Vital Signs

Vital signs (pulse rate, blood pressure [systolic/diastolic], and respiratory rate) will be measured at the time points detailed in Table 1. All vital sign results outside of the reference ranges will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

Before blood pressure and pulse are measured, the patient must rest in a supine or seated position for at least 5 minutes. The same position and arm should be used each time vital signs are measured for a given patient. For any abnormal vital signs value, the measurement should be repeated as soon as possible. Any vital signs value that is judged by the investigator as clinically significant will be recorded both on the source documentation and the CRF as an adverse event, and monitored as described in Section 7.1.2.

7.6. Electrocardiography

A 12-lead ECG will be performed at the time points detailed in Table 1.

The ECG will be interpreted locally by the principal investigator (or qualified physician). All ECG results will be judged by the investigator (or qualified physician) as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

Any ECG finding that is judged by the investigator (or qualified physician) as clinically significant (except at the screening visit) will be considered an adverse event, recorded on the source documentation and in the CRF, and monitored as described in Section 7.1.2.

7.7. Assessment of Local Tolerability and Pain

Local tolerability at the injection site (erythema, ecchymosis, induration, tenderness, warmth, and swelling, and pain) will be assessed, using standardized scales. Patient reported pain at the injection site will be reported using a standardized 11-point pain intensity numerical response scale (NRS-11) where 0 is “No pain” and 10 is “Worst possible pain”, and patients will be asked to respond to the following question: “How much pain do you feel at the drug injection site?”.

The assessments will be performed 1 hour±10 minutes after IMP administration (Table 1).

Severity of local tolerability symptoms should be assessed as described in Table 5. Erythema, ecchymosis, and induration will be considered only if they reach a diameter of at least 5 mm. The surface diameter in millimeters should be recorded and erythema, induration, and ecchymosis at the injection site will be graded according to the diameter measurements: Absent, 5 mm to ≤50 mm (mild), >50 to ≤100 mm (moderate), and >100 mm (severe). Induration must be assessed by careful superficial palpation avoiding pressuring or squeezing the injection site.

In the case that symptoms do not resolve, assessments will proceed as long as the patient remains at the study center, and thereafter at each ambulatory visit. Appropriate treatment may be provided if necessary, in which case it must be recorded as concomitant medication.

Table 5: Severity Assessment of Local Tolerability

Test	Response
Erythema	- Absent - Erythema surface diameter 5 mm to ≤50 mm (mild) - Erythema surface diameter >50 to ≤100 mm (moderate) - Erythema surface diameter >100 mm (severe)
Ecchymosis	- Absent - Ecchymosis surface diameter 5 mm to ≤50 mm (mild) - Ecchymosis surface diameter >50 to ≤100 mm (moderate) - Ecchymosis surface diameter >100 mm (severe)
Induration	- Absent - Induration surface diameter 5 mm to ≤50 mm (mild) - Induration surface diameter >50 to ≤100 mm (moderate) - Induration surface diameter >100 mm (severe)
Tenderness Warmth Swelling	- None - Mild - Moderate - Severe

Injection site findings will not be captured as adverse events unless they fulfill characteristics that are beyond those in the specified forms/scales (eg, necrosis, abscess, etc) or fulfill seriousness criteria and then they must be recorded and reported as specified in Section 7.1.2.

7.8. Pregnancy

This study is conducted in postmenopausal women. However, any female patient becoming pregnant during the study will discontinue IMP and will be discontinued from the study. The process for reporting a pregnancy is the same as that for reporting a serious adverse event but using the pregnancy form. Pregnant patients will be monitored for the outcome of the pregnancy (including spontaneous, elective, or voluntary abortion). If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including details of birth and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the sponsor. Any complication of pregnancy will be reported as an adverse event or serious adverse event, as appropriate.

7.9. Medication Error and Special Situations Related to the Investigational Medicinal Products

Any administration of IMP that is not in accordance with the study protocol should be reported as a protocol deviation and in the patients' source documents, regardless of whether or not an adverse event occurs as a result.

The following are types of medication errors and special situations:

1. Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer.
2. Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the protocol or authorized product information. Clinical judgment should always be applied. Any dose of IMP (whether the test or reference IMP), whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor.
3. Misuse: Situations where the IMP is intentionally and inappropriately used not in accordance with the protocol or authorized product information.
4. Abuse: Persistent or sporadic, intentional excessive use of IMP which is accompanied by harmful physical or psychological effects.
5. Off-label use: Situations where an IMP is intentionally used for a medical purpose not in accordance with the protocol or authorized product information.

Occupational exposure: Exposure to an IMP, as a result of one's professional or non-professional occupation.

8. ASSESSMENT OF PHARMACOKINETICS AND IMMUNOGENICITY

8.1. Pharmacokinetic Assessment

Blood samples (4 mL) will be collected via venipuncture or indwelling catheter before and up to 78 weeks after TVB-009P or PROLIA US administration at the time points detailed in Table 1 for measurements of serum concentration of TVB-009P and PROLIA US. The dates and times of IMP administration and the date and time point (24-hour clock time) of each pharmacokinetic sample will be recorded both on the source documentation and the CRF.

Samples will be analyzed for concentration of TVB-009P and PROLIA US using an appropriate validated method. Incurred sample reanalysis may be performed (see Appendix I).

Details on sample handling, storage, shipment, and analysis are given in the pharmacy manual.

8.2. Immunogenicity Testing

Blood samples (5 mL) for assessment of ADA response will be collected via venipuncture or indwelling catheter before and up to 78 weeks after TVB-009P or PROLIA US administration at the time points detailed in Table 1.

Additionally, efforts should be made to collect ADA samples when a severe hypersensitivity reaction (eg, anaphylaxis) is suspected, serious adverse event, or immunogenicity-related adverse event is observed as close to onset of the event as possible, resolution of event, and 30 days following the event onset, if possible.

When a number of assessments are to be conducted at the same time point, the immunogenicity blood sample should be taken after other assessments but before IMP administration. The dates and times of IMP administration and the date and time point of each immunogenicity sample will be recorded both on the source documentation and the CRF.

The detection and characterization of antibodies to TVB-009P and PROLIA US will be performed using validated methods by the bioanalytical lab (Appendix A). Immunogenicity assessment by the detection of ADA levels in serum samples will be performed using the same validated assay, employing a 3-tiered approach. Briefly, all samples will be screened for ADA using bridging enzyme-linked immunosorbent assay (ELISA) with labeled TVB-009P, the screening positive samples will be analyzed in a confirmatory assay, and the confirmed ADA positive samples will be tested for antibody titer determination. The characterization of confirmed ADA positive samples will include analysis for neutralization potential.

Samples may be stored if permitted by the ICF and local regulations after the last patient's last visit for the study to enable potential reanalysis of immune responses to TVB-009P (see Appendix J).

Details on sample handling, storage, shipment, and analysis are given in the study laboratory manual.

9. STATISTICS

This section describes the statistical analysis as foreseen at the time of planning the study. Changes, additions, and further details about the analyses will be described in the statistical analysis plan (SAP). After finalization of the SAP, any additional analyses or changes to analyses that may be required will be fully disclosed in the clinical study report.

9.1. Sample Size and Power Considerations

9.2. Analysis Sets

9.2.1. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all randomized patients.

In the ITT analysis set, treatment will be assigned based on the treatment to which patients were randomized in the main treatment period, regardless of which treatment they actually received.

9.2.2. Modified Intent-to-Treat Analysis Set

The modified intent-to-treat (mITT) analysis set is a subset of the ITT analysis set including only patients who received at least 1 dose of IMP and had at least 1 post-baseline evaluation of LS-BMD.

Patients who withdraw from the study prior to week 26 will not have a post-baseline LS-BMD measurement, and will therefore not be included in the mITT analysis set.

In the mITT analysis set, treatment will be assigned based on the treatment to which patients were randomized in the main treatment period, regardless of which treatment they actually received.

9.2.3. Safety Analysis Set

The safety analysis set will include all patients who received at least 1 dose of IMP.

In the safety analysis set, treatment will be assigned based on the treatment patients actually received in the main treatment period, regardless of the treatment to which they were randomized. Rules for assignment of treatment in case of actual treatment error will be provided in the SAP.

9.2.4. Per-Protocol Analysis Set

The per-protocol (PP) analysis set is a subset of the mITT analysis set including only patients who received treatment with IMP at the baseline and week 26 visit as randomized and completed the main treatment period without any major protocol deviations that may impact the similarity assessments of LS-BMD and sCTX-1.

Rules for excluding patients from the PP analysis set will be provided in the SAP. Evaluation of exclusion from the PP analysis set will be discussed on a case-by-case basis and documented prior to DBL and unblinding of the study for final analysis.

9.2.5. Transition Intent-to-treat Analysis Set

The transition intent-to-treat (TITT) analysis set will include all patients randomized in the transition period.

In the TITT analysis set, treatment will be assigned based on the treatment to which patients were randomized in the main and transition treatment periods, regardless of which treatment they actually received.

9.2.6. Transition Modified Intent-to-treat Analysis Set

The transition modified intent-to-treat (TmITT) analysis set will include all patients who received the third dose of IMP and had an EOS evaluation of LS-BMD.

In the TmITT analysis set, treatment will be assigned based on the treatment to which patients were randomized in the main and transition treatment periods, regardless of which treatment they actually received.

9.2.7. Transition Safety Analysis Set

The transition safety analysis set will include all patients who received the third dose of IMP.

In the transition safety analysis set, treatment will be assigned based upon the treatment patients actually received in the main and transition periods, regardless of the treatment to which they were randomized. Rules for assignment of treatment in case of actual treatment error will be provided in the SAP.

9.3. Data Handling Conventions

For all descriptive statistics, only the observed data from the patients will be used.

9.3.1. Handling Withdrawals and Missing Data

Missing LS-BMD or sCTX-1 assessments (either due to withdrawal from the study or for other reasons) are assumed to be missing at random (MAR) in this efficacy and safety biosimilar study in PMO.

The mITT analysis set will be used for the primary analysis. This analysis set includes only patients that had at least 1 post-baseline evaluation of LS-BMD (see Section 9.2.2), ie, reached week 26; the drop-out rate prior to week 26 is assumed to be low, [redacted] Underlying assumptions are that the drop-out rate prior to week 26 will be similar in both treatment groups, and that drop-outs are not related to efficacy. As both treatment groups are active, and improvement in the underlying disease is not expected to be felt by the patient, these assumptions are considered reasonable. The assumption that drop-out rates are comparable between the treatment groups will be assessed using descriptive statistics (see Section 9.4.1).

In the primary analysis, missing LS-BMD at week 52 will be imputed based on post-baseline assessments using multiple imputation under the MAR assumption (see Section 9.5.4); this is a conservative approach for similarity testing, as missing data will be imputed within each treatment group separately.

Since the mITT analysis set includes only patients that reached at least week 26, missing sCTX-1 at week 26 is expected to be negligible and will not be imputed.

Sensitivity and supplementary analyses for missing data in the primary analysis are presented in Section 9.5.4.1 and Section 9.5.4.2.

9.3.2. Handling Below the Limit of Quantitation

sCTX-1 and P1NP values below limit of quantitation (BLQ) will be imputed by the lower limit of quantitation (LLOQ); 0.033 ng/mL for sCTX-1 and 1.0 ng/mL for P1NP).

Sensitivity analysis for BLQ imputation in the analysis of sCTX-1 percent change from baseline at week 26 is presented in Section 9.5.4.1.

9.4. Study Population

The ITT analysis set (Section 9.2) will be used for all study population summaries unless otherwise specified. Summaries will be presented by treatment group and for all patients.

9.4.1. Patient Disposition

The number of patients screened, patients screened but not randomized, and patients in the main treatment period and the transition period will be summarized using descriptive statistics.

For the main treatment period, the summary will include: patients randomized (ITT analysis set), patients in the mITT, safety, and PP analysis sets, patients that withdraw up to week 26, patients that withdraw after week 26, and patients that complete the main treatment period.

For the transition period, the summary will include: patients randomized (TITT analysis set), patients in the TmITT and transition safety analysis sets, patients that withdraw during the transition period, and patients that complete the study.

Data from patients who withdraw from the study will also be summarized by reason for withdrawal as recorded in the disposition CRF using descriptive statistics.

If more than 10% of the patients withdraw from the study before the end of the main treatment period, the number of days until study discontinuation will be analyzed using Kaplan-Meier methodology. In case of imbalance in withdrawal rates between treatment groups, further analysis to explore if the imbalance can be attributed to differences in baseline characteristics may be conducted as deemed necessary.

9.4.2. Demographic and Baseline Characteristics

Patient demographic and baseline characteristics, including but not limited to, medical history, prior medications and therapies, and ECG findings, will be summarized using descriptive statistics.

9.5. Efficacy and Pharmacodynamic Analysis

The mITT analysis set will be used as the primary analysis set for efficacy and pharmacodynamics analysis in the main treatment period. The ITT and PP analysis sets will be used for supplementary analyses.

The TmITT analysis set will be used as the primary analysis set for efficacy and pharmacodynamics in the transition period.

9.5.1. Primary Endpoint

The primary efficacy endpoint for the US filing is the percent change from baseline in LS-BMD at week 52, mean difference between TVB-009P and PROLIA US treatment groups.

The co-primary endpoints for the EU filing are: (1) percent change from baseline in LS-BMD at week 52, mean difference between TVB-009P and PROLIA US treatment groups; (2) percent change from baseline in sCTX-1 at week 26, mean difference between TVB-009P and PROLIA US treatment groups.

9.5.2. Secondary Endpoints

The secondary efficacy and pharmacodynamic endpoints are the mean difference between TVB-009P and PROLIA US treatment groups in:

- percent change from baseline in LS-BMD at week 26 by DXA
- percent change from baseline in femoral neck BMD by DXA at week 26 and at week 52
- percent change from baseline in total hip BMD by DXA at week 26 and at week 52
- percent change from baseline in sCTX-1 at all time points
- sCTX-1 suppression at week 4

- percent change from baseline in P1NP at week 26 and week 52
- incidence of fractures up to week 52

9.5.3. Efficacy and Pharmacodynamic Endpoints in the Transition Period

The pharmacodynamic/efficacy endpoints in the transition period are the mean difference between TVB-009P and PROLIA US treatment groups in:

- percent change from week 52 in LS-BMD by DXA at week 78
- difference between percent change from baseline in sCTX-1 between week 52 and week 78
- percent change from week 52 in femoral neck BMD by DXA at week 78
- percent change from week 52 in total hip BMD by DXA at week 78
- difference between percent change from baseline in P1NP between week 52 and week 78
- incidence of fractures up to week 78

9.5.4. Primary Efficacy Analysis

The primary analysis of LS-BMD percent change from baseline at week 52 is an analysis of covariance (ANCOVA) model [redacted] Similarity will be demonstrated if the 95% CI for the mean difference between TVB-009P and PROLIA US falls entirely within the similarity margin of ±1.45%.

The primary analysis of sCTX-1 percent change from baseline at week 26 is an ANCOVA model [redacted]. Similarity will be demonstrated if the 95% CI for the mean difference between TVB-009P and PROLIA US falls entirely within the similarity margin of ±20%.

The primary analysis will be based on the mITT analysis set, which will include all patients who received at least 1 dose of IMP, as randomized, and had data for at least 1 post-baseline central reader evaluation of LS-BMD by DXA.

Patients who withdraw from the study prior to week 26 will not have a post-baseline LS-BMD measurement, and will therefore not be included in the mITT analysis set. For patients who withdraw from the study between week 26 and week 52 and have a post-baseline LS-BMD measurement at week 26 and/or early termination (ET), the percent change from baseline in LS-BMD at week 52 will be imputed using the predictive mean matching multiple imputation method (Heitjan and Little 1991, Schenker and Taylor 1996), for each treatment arm separately (MAR assumption). The imputation model will include baseline LS-BDM value, body weight at baseline, region (US/non-US), previous use of bisphosphates (yes/no), and the last available post-baseline LS-BMD percent change from baseline value. The resulting complete, imputed datasets will each be analyzed using the same model as the primary analysis model, and the resulting statistics combined using methodology provided by Rubin (1987) and Little and Rubin (2002).

For the primary analysis of s-CTX-1 percent change from baseline at week 26, values BLQ will be imputed as the LLOQ.

9.5.4.1. Sensitivity/Supportive Analysis for the Primary Analysis

To assess the robustness of the primary efficacy analysis using the same estimand, sensitivity analyses will include:

Sensitivity analyses for the statistical model:

- primary model, including only treatment group as a covariate

Sensitivity analysis for BLQ imputation:

For the primary analysis of s-CTX-1 percent change from baseline at week 26, values below BLQ will be imputed as the LLOQ. Sensitivity analyses for this imputation will be performed as follows:

- two-dimensional tipping-point: for the analysis of sCTX-1 percent change from baseline at week 26, sensitivity analysis for the BLQ imputation will be conducted by repeating the analysis using different imputed values for patients in the TVB-009P group and the PROLIA US group, in the range of 0 to LLOQ (0.033 ng/mL).

9.5.4.2. Supplementary Analysis for the Primary Analysis

Supplementary analyses to evaluate effect of assumptions on missing data on the results:

- two-dimensional tipping point (missing not at random [MNAR]): in order to assess the sensitivity of the primary analysis to the MAR assumption on missing data for patients that have at least 1 post-baseline value, supplementary analysis for the primary analysis will be conducted using multiple imputation under MNAR assumption. In this analysis, missing LS-BMD percent change from baseline at week 52 will be imputed using the same predictive mean matching multiple imputation method as in the primary analysis, adjusted under MNAR assumption:
  - the percent change from baseline in LS-BMD at week 52 in patients randomized to TVB-009P with missing LS-BMD at week 52 will be imputed assuming the treatment effect is worsened by δ_1 compared to the patients who have no missing value (where δ_1 = 0 to 2% or estimated treatment effect the TVB-009P group, whichever is higher);
  - the percent change from baseline in LS-BMD at week 52 in patients randomized to PROLIA US with missing LS-BMD at week 52 will be imputed assuming the treatment effect is worsened by δ_2 compared to the patients who have no missing value (where δ_2 = 0 to 2% or estimated treatment effect the PROLIA US group, whichever is higher);

  The resulting complete, imputed datasets will each be analyzed using the same model as the primary analysis model, and the resulting statistics combined using methodology provided by Rubin (1987) and Little and Rubin (2002).

- to further alleviate the concern on the uncertainty introduced by missing data, the following 2 separate 1-sided tests of alpha=0.05 with missing data imputed under the corresponding null using a multiple imputation method will be conducted:
  - in the first test, missing values for the TVB-009P group will be imputed under the non-inferiority null (the lower boundary of the equivalence margin, -1.45%) for testing whether it is non-inferior to PROLIA US;
  - in the second test, missing values for the TVB-009P group will be imputed under the non-superiority null (+1.45%) for testing whether it is non-superior to PROLIA US.

  The resulting complete, imputed datasets will each be analyzed using the same model as the primary analysis model, and the resulting statistics combined using methodology provided by Rubin (1987) and Little and Rubin (2002).
- primary analysis repeated on the ITT analysis set
- two dimensional tipping point (MNAR) repeated on the ITT analysis set

Other analyses:

- primary model repeated for the PP analysis set
- primary model repeated for the mITT analysis set, excluding patients who received IMP not as randomized at baseline and/or at week 26

9.5.4.3. Secondary Efficacy and Pharmacodynamic Analysis

No formal hypothesis testing is planned for the secondary efficacy and pharmacodynamic endpoints.

Descriptive statistics will be presented by treatment group. For descriptive purposes, 95% CIs for the difference in mean (for continuous variables) or proportion (for binary variables) between treatment groups will be presented.

For vertebral fractures, incidence of patients with new vertebral fractures and incidence of patients with new non-vertebral fractures will be summarized.

9.5.4.4. Efficacy and Pharmacodynamic Analysis in the Transition Period

No formal hypothesis testing is planned for the efficacy and pharmacodynamic endpoints in the transition period.

The efficacy analyses in the transition period will be based on the TmITT analysis set, which will include all patients who received the third dose of IMP and had an EOS evaluation of LS-BMD.

Descriptive statistics will be presented by the treatment groups to which the patients were assigned in the main and transition periods (PROLIA US/PROLIA US, PROLIA US/TVB-009P, and TVB-009P/TVB-009P). In addition, the difference and 95% CI for the difference between the PROLIA US/PROLIA US and PROLIA US/TVB-009P treatment groups will be presented.

9.6. Multiple Comparisons and Multiplicity

Formal statistical analysis of similarity will be performed only on the following endpoints:

(1) percent change from baseline to week 52 in LS-BMD

(2) percent change from baseline in sCTX-1 at week 26

For the US filing, percent change from baseline to week 52 in LS-BMD is the primary endpoint. Percent change from baseline in sCTX-1 at week 26 is a secondary endpoint. For this submission, the percent change from baseline in sCTX-1 at week 26 will be tested only if the primary endpoint was found to be statistically similar (ie, met the similarity criteria).

For the EU submission, percent change from baseline in LS-BMD at week 52 and percent change from baseline in sCTX-1 at week 26 are co-primary endpoints. For this submission, success will be declared if similarity is demonstrated for both co-primary endpoints.

The analysis of all other endpoints will be descriptive, therefore no control for multiplicity is needed.

9.7. Safety Analysis

Safety analyses will be performed on the safety analysis set and the transition safety analysis set (Section 9.2.3 and Section 9.2.7).

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). In the summary tables each patient will be counted only once in each preferred term (PT) or system organ class (SOC) category for the analyses of safety. Summaries will be presented for all treatment emergent adverse events (overall and by severity), adverse events determined by the investigator to be related to IMP/device (ie, reasonable possibility) (defined as related or with missing relationship) (overall and by severity), serious adverse events, and adverse events causing withdrawal from the study. Summaries will be presented by treatment group and for all patients. For all adverse events and for serious adverse events, the summaries will include number of events as well as number and percent of patients with events. Patient listings of all adverse events, serious adverse events, and adverse events leading to withdrawal will be presented.

Values and change from baseline in laboratory and vital signs data will be summarized descriptively.

All prior/concomitant medications will be coded using WHODrug Global. The use of concomitant medications will be summarized by therapeutic class using descriptive statistics.

Local tolerability findings will be summarized using descriptive statistics.

For continuous variables, descriptive statistics will be provided for actual values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided.

Incidence in abnormalities in laboratory, ECG and vital signs data will be summarized descriptively.

If any patient dies during the study, all relevant information will be discussed in the patient narrative included in the CSR; a listing of any deaths during the study will be provided.

9.7.1. Safety Analysis in the Main Treatment Period

Safety analyses in the main treatment period will be performed on the safety analysis set. Summaries will be presented by treatment group (TVB-009P, PROLIA US) and for all patients.

Summaries of adverse events in the main treatment period will be presented.

All safety variables at the week 52 visit that are assessed prior to administration of the third dose of IMP will be considered as occurring during the main treatment period.

9.7.2. Safety Analysis in the Transition Period

Safety analyses in the transition period will be performed on the transition safety analysis set. Summaries of adverse events starting in the transition period will be presented. The analyses will include patients in the PROLIA US/TVB-009P, TVB-009P/TVB-009P and PROLIA US/PROLIA US treatment groups.

9.7.3. Safety Analysis in the Overall Treatment Period

Safety analyses in the overall treatment period will be performed on the safety analysis set. The analyses will include only patients in the PROLIA US/PROLIA US and TVB-009P/TVB-009P treatment groups.

The analyses will be similar to the analyses of the main treatment period. Summaries will be presented by treatment group (PROLIA US, TVB-009P) and for all patients included in the analysis.

9.8. Pharmacokinetic Analysis

The following exploratory pharmacokinetic parameters will be summarized using descriptive statistics:

- serum concentration before next dose (C_{trough}), before second and third dose, and 6 months after third dose
- serum concentration at 2 weeks postdose (C_{2weeks})

Details of the pharmacokinetic analysis of the area under the curve over the dosing period ($AUC_{0\text{-}tau}$) after first dose derived from population pharmacokinetics analysis, C_{trough} before second dose derived from population pharmacokinetics analysis, and C_{max} after first dose derived from population pharmacokinetic analysis will be given in a separate TVB-009P population pharmacokinetic statistical analysis plan. The results of the population pharmacokinetic analysis will be provided in a separate report.

9.9. Immunogenicity Analysis

The immunogenicity analysis will be performed after completion of the main treatment period at week 52 for the of TVB-009P and PROLIA US treatment groups and after the completion of the transition period at week 78 (EOS) for TVB-009P and PROLIA US/TVB-009P treatment groups.

Results of immunogenicity assessment will be listed.

If more than 5 patients develop ADA anytime post-baseline, the incidence of ADA positive will be summarized by treatment group, and ADA positive/negative, titer level, and neutralizing ADA positive/negative will be summarized at each visit using descriptive statistics.

The effect of positive immunogenicity findings on efficacy and safety may be investigated, if applicable.

9.10. Sequence of Final Analyses

Upon completion of the main treatment period (up to and including week 52) the sponsor will unblind the main treatment period (up to and including week 52; not including third IMP dosing and assessments following the third dosing), while keeping the investigators (and other site staff involved in study assessments) and the patients blinded (see Section 5.9.2). A CSR that contains the results of the analysis of the main treatment period (up to and including week 52) will be submitted with the filing of the Biologics License Application (BLA) and/or Marketing Authorisation Application (MAA). The results of the analysis of the transition period (up to and including week 78) will be included in a CSR addendum that is planned to be submitted in the BLA or during the 4-Month Safety Update after filing of the BLA and at the earliest opportunity during the MAA procedure.

9.11. Reporting Deviations from the Statistical Plan

Deviations from the statistical plan, along with the reasons for the deviations, will be described in protocol amendments, the SAP, the CSR, or any combination of these, as appropriate, and in accordance with applicable national, local, and regional requirements and regulations.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Refer to Appendix C for information regarding quality control and quality assurance. This includes information about protocol amendments, protocol deviations, responsibilities of the investigator to study personnel, study monitoring, and audit and inspection.

Refer to Appendix H for the definition of a clinical product complaint and investigator responsibilities in the management of a clinical product complaint.

11. COMPLIANCE STATEMENT

This study will be conducted in full accordance with the ICH Harmonised Tripartite Guideline, Guideline for GCP E6 and any applicable national and local laws and regulations (eg, Title 21 Code of Federal Regulations [21CFR] Parts 11, 50, 54, 56, 312, and 314, Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use). Any episode of noncompliance will be documented.

The investigator is responsible for performing the clinical study in accordance with this protocol and the applicable GCP guidelines referenced above for collecting, recording, and reporting the data accurately and properly. Agreement of the investigator to conduct and administer this clinical study in accordance with the protocol will be documented in separate clinical study agreements with the sponsor and other forms as required by national competent authorities in the country where each investigational center is located.

The investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the clinical study; and must ensure that trained personnel are immediately available in the event of a medical emergency. The investigator and the involved clinical study personnel must be familiar with the background and requirements of the study; and with the properties of the IMPs as described in the IB or prescribing information.

The principal investigator at each investigational center has the overall responsibility for the conduct and administration of the clinical study at that investigational center and for contacts with study management, with the IEC/IRB, and with competent authorities.

See Appendix D for the ethics expectations of informed consent, competent authorities and IEC and IRB, confidentiality regarding study patients, and requirements for registration of the clinical study.

12. DATA MANAGEMENT AND RECORD KEEPING

See Appendix K for information regarding data management and record keeping. This includes direct access to source data and documents, data collection, data quality control, and archiving of CRFs and source documents.

13. FINANCING AND INSURANCE

A separate clinical study agreement, including a study budget, will be signed between each principal investigator and the sponsor (or the CRO designated by the sponsor) before the IMP is delivered.

The patients in this clinical study are insured in accordance with applicable legal provisions. The policy coverage is subject to the full policy terms, conditions, extensions, and exclusions. Excluded from the insurance coverage are eg, damages to health, and worsening of previous existing disease that would have occurred or continued if the patient had not taken part in the clinical study.

The policy of Clinical Trials Insurance will be provided to the investigational centers by the sponsor.

For covered clinical studies (see 21CFR54), the investigator will provide the sponsor with financial information required to complete FDA 3454 form. Each investigator will notify the sponsor of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

14. PUBLICATION POLICY

See Appendix L for information regarding the publication policy.

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16. SUMMARY OF CHANGES TO THE PROTOCOL

16.1. Protocol Amendment 02 dated 29 June 2021

The primary reason for this global amendment is to implement changes requested by FDA and also to implement the changes from Local Amendment 01 (Section 16.2) globally. All major changes to the protocol body are listed below in the table and are reflected in the synopsis and Table 1 (Study Procedures and Assessments), as applicable. Minor editorial changes have been made.

Original text with changes shown	New wording	Reason/Justification for change
3. STUDY DESIGN		
Section 3.5, Table 1; other Section affected by this change: Appendix B (visit 12)		
Footnote q In case of early termination, LS BMD DXA, total hip and femoral neck BMD DXA, and lateral spine X ray will be assessed only in patients who terminate the study between the week 26 and week 52 visits. The minimum time between two DXA scans should be 3 months. These assessments will not be performed for patients who terminate the study earlier than week 26 or during the transition period.	*Footnote q* In case of early termination, LS BMD DXA, total hip and femoral neck BMD DXA, and lateral spine X ray will be assessed only in patients who terminate the study between the week 26 and week 52 visits. The minimum time between two DXA scans should be 3 months. These assessments will not be performed for patients who terminate the study earlier than week 26 or during the transition period.	Specified minimum time between two DXA scans
4. SELECTION AND WITHDRAWAL OF PATIENTS		
Section 4.3		
Each patient is free to withdraw from the study at any time, without prejudice to their continued care. Patients must be withdrawn from the study if any of the following events occur: 1. Patient withdraws consent or requests withdrawal from the study for any reason. 2. Patient is noncompliant with the study procedures and assessments in the opinion of the investigator. 3. The sponsor requests withdrawal of the patient. 4. Patient experiences an adverse event or other medical condition which indicates to the investigator that continued participation is not in the best interest of the patient, for example, but not limited to osteonecrosis of the jaw, atypical subtrochanteric and diaphyseal femoral fractures, serious infections, severe dermatologic adverse reactions or severe musculoskeletal pain. … Investigators should attempt to obtain information on patients in the case of withdrawal from the study. Results of any evaluations and observations, together with a narrative describing the reason(s) for withdrawal from the study, must be recorded in the source documents. The case report form (CRF) must document	Each patient is free to withdraw from the study at any time, without prejudice to their continued care. Patients must be withdrawn from the study if any of the following events occur: 1. Patient withdraws consent or requests withdrawal from the study for any reason. 2. Patient is noncompliant with the study procedures and assessments in the opinion of the investigator. 3. The sponsor requests withdrawal of the patient. 4. Patient experiences an adverse event or other medical condition which indicates to the investigator that continued participation is not in the best interest of the patient, for example, but not limited to osteonecrosis of the jaw, atypical subtrochanteric and diaphyseal femoral fractures, serious infections, severe dermatologic adverse reactions or severe musculoskeletal pain. … Investigators should attempt to obtain information on patients in the case of withdrawal from the study. Results of any evaluations and observations, together with a narrative describing the reason(s) for withdrawal from the study, must be	Included examples for events leading to study discontinuation and provided instructions for the management of BMD reduction of more than 7% from baseline

Original text with changes shown	New wording	Reason/Justification for change
the primary reason for withdrawal from the study. If a patient experiences a BMD reduction of more than 7% from baseline at any time during the study, the investigator needs to discuss with the patient the implications for her fracture risk, alternative treatment options and the option for continuing in the study and to document that discussion and the decision made. If alternative treatment is recommended further study drug administration should be discontinued and every effort should be taken to complete remaining study visits in the main treatment period, regardless of the type of alternative treatment chosen by the subject. If a patient exhibits clinical symptoms that may indicate COVID-19 infection after entering the study, the patient should be tested for active COVID-19 infection...	recorded in the source documents. The case report form (CRF) must document the primary reason for withdrawal from the study. If a patient experiences a BMD reduction of more than 7% from baseline at any time during the study, the investigator needs to discuss with the patient the implications for her fracture risk, alternative treatment options and the option for continuing in the study and to document that discussion and the decision made. If alternative treatment is recommended further study drug administration should be discontinued and every effort should be taken to complete remaining study visits in the main treatment period, regardless of the type of alternative treatment chosen by the subject. If a patient exhibits clinical symptoms that may indicate COVID-19 infection after entering the study, the patient should be tested for active COVID-19 infection...	
Section 4.5, other Section affected by this change: Section 3.5 (Table 1)		
A patient with a screening serum 25 hydroxy (OH) vitamin D level ~~<~~≤20 ng/mL may be rescreened once to re evaluate vitamin D level post repletion. Patients with albumin adjusted serum calcium outside the normal range, as assessed by the central laboratory, may be rescreened once to re evaluate calcium levels. Informed consent obtained at the beginning of the screening period also covers the partial rescreening for low vitamin D or for calcium; therefore reconsenting is not required.	A patient with a screening serum 25 hydroxy (OH) vitamin D level ≤20 ng/mL may be rescreened once to re evaluate vitamin D level post repletion. Patients with albumin adjusted serum calcium outside the normal range, as assessed by the central laboratory, may be rescreened once to re evaluate calcium levels. Informed consent obtained at the beginning of the screening period also covers the partial rescreening for low vitamin D or for calcium; therefore reconsenting is not required.	Correction (per inclusion criterion h patients have to have a serum 25 (OH) vitamin D level >20 ng/mL at screening)
5. TREATMENTS		
Section 5.1.3		
Patients will be instructed to take 1000 mg calcium daily and at least 400 IU vitamin D daily from screening to week 78 (EOS). Calcium and vitamin D will be provided from local sources. If hypocalcemia is detected, and there is no additional underlying reason, ~~the investigator may decide to treat with additional calcium supplementation if appropriate.~~ this should be further monitored and the below can be used for the corrective treatment:	Patients will be instructed to take 1000 mg calcium daily and at least 400 IU vitamin D daily from screening to week 78 (EOS). Calcium and vitamin D will be provided from local sources. If hypocalcemia is detected, and there is no additional underlying reason, this should be further monitored and the below can be used for the corrective treatment: • Mild to moderate hypocalcemia (≥ 7.5 mg/dL,	Included instructions for the management of hypocalcemia and hypercalcaemia

Original text with changes shown	New wording	Reason/Justification for change
• Mild to moderate hypocalcemia (≥ 7.5 mg/dL, < 8.4 mg/dL adjusted calcium): calcium, up to 3000 mg/day (oral) at the discretion of the investigator • Symptomatic hypocalcemia or severe asymptomatic hypocalcemia (< 7.5 mg/dL adjusted calcium): intravenous calcium followed by oral calcium at the discretion of the investigator. In case of continuous symptomatic or severe asymptomatic hypocalcemia the investigator should consider to postpone study drug administration by a maximum of 2 months and should discuss the situation with the medical monitor. If hypercalcaemia is detected, supplementation with calcium and vitamin D should be interrupted and calcium levels should be further monitored; severe hypercalcaemia might be treated (eg, calcitonin or calcimimetics) at the discretion of the investigator. Patients will be allowed to continue treatment with study drug.	< 8.4 mg/dL adjusted calcium): calcium, up to 3000 mg/day (oral) at the discretion of the investigator • Symptomatic hypocalcemia or severe asymptomatic hypocalcemia (< 7.5 mg/dL adjusted calcium): intravenous calcium followed by oral calcium at the discretion of the investigator. In case of continuous symptomatic or severe asymptomatic hypocalcemia the investigator should consider to postpone study drug administration by a maximum of 2 months and should discuss the situation with the medical monitor. If hypercalcaemia is detected, supplementation with calcium and vitamin D should be interrupted and calcium levels should be further monitored; severe hypercalcaemia might be treated (eg, calcitonin or calcimimetics) at the discretion of the investigator. Patients will be allowed to continue treatment with study drug.	
Section 5.8 (last paragraph)		
At the investigational center, only the pharmacist or designee who will dispense the study drug and the study drug administrator will be unblinded. These staff will not participate in any efficacy, pharmacokinetic, pharmacodynamic, immunogenicity, and safety assessments.	At the investigational center, only the pharmacist or designee who will dispense the study drug and the study drug administrator will be unblinded. These staff will not participate in any efficacy, pharmacokinetic, pharmacodynamic, immunogenicity, and safety assessments.	Clarified that staff involved in study drug preparation/administration will not be involved in any study assessments
6. ASSESSMENT OF EFFICACY AND PHARMACODYNAMICS		
Section 6.1.1, other Section affected by this change: 6.1.2		
LS-BMD will be measured by DXA. Hologic and GE Lunar DXA machines will be used and the same machine should be used for all study procedures for a particular patient for the duration of the study. DXA machine changes during the study are strongly discouraged; however, if a machine is changed during the study, the central imaging vendor will oversee the change in order to minimize the impact on assessments of BMD change. All LS-BMD DXA scans will be submitted to and analyzed by	LS-BMD will be measured by DXA. Hologic and GE Lunar DXA machines will be used and the same machine should be used for all study procedures for a particular patient for the duration of the study. DXA machine changes during the study are strongly discouraged; however, if a machine is changed during the study, the central imaging vendor will oversee the change in order to minimize the impact on assessments of BMD change. All LS-BMD DXA scans will be submitted to and	Clarified that DXA results after start of treatment will be provided to the investigator after study completion

Original text with changes shown	New wording	Reason/Justification for change
the central imaging vendor. The results of the DXA scans after start of treatment will be provided to the investigator after completion of the study (after week 78) and DBL upon request of the patient and/or due to country regulation. Lumbar spine scans must include L1 through L4. The vertebrae on which the measurement is based should be consistent throughout the study on an individual patient level. …	analyzed by the central imaging vendor. The results of the DXA scans after start of treatment will be provided to the investigator after completion of the study (after week 78) and DBL upon request of the patient and/or due to country regulation. Lumbar spine scans must include L1 through L4. The vertebrae on which the measurement is based should be consistent throughout the study on an individual patient level. …	
Section 6.1.2; other Section affected by this change: Section 3.5 (Table 1)		
Total hip and femoral neck BMD will be measured by DXA. These scans will be unilateral only. For each patient, the same hip should be scanned throughout the study. Hologic and GE Lunar DXA machines will be used and the same machine must be used for all study procedures for a particular patient for the duration of the study. All hip and femoral neck bone DXA scans will be submitted to and analyzed by the central imaging vendor. …	Total hip and femoral neck BMD will be measured by DXA. These scans will be unilateral only. For each patient, the same hip should be scanned throughout the study. Hologic and GE Lunar DXA machines will be used and the same machine must be used for all study procedures for a particular patient for the duration of the study. All hip and femoral neck bone DXA scans will be submitted to and analyzed by the central imaging vendor. …	Specified that total hip and femoral neck BMD will be measured by unilateral DXA
Section 6.1.3, other Section affected by this 6.1.4		
Patients will undergo a lateral spine X-ray for assessment of vertebral fractures by the central imaging vendor. Nominally, vertebral fracture will be assessed in all vertebrae from the fourth thoracic vertebra (T4) to the fourth lumbar vertebra (L4). Any new fracture should be reported as an adverse event (Section 7.1.2).	Patients will undergo a lateral spine X-ray for assessment of vertebral fractures by the central imaging vendor. Nominally, vertebral fracture will be assessed in all vertebrae from the fourth thoracic vertebra (T4) to the fourth lumbar vertebra (L4). Any new fracture should be reported as an adverse event (Section 7.1.2).	Clarified that any new fracture should be reported as an adverse event.
7. ASSESSMENT OF SAFETY		
Section 7.3.2, other sections affected by this change: Table 1 in Section 3 and Appendix B (visit 2)		
Added new subsection for urine pregnancy test: 7.3.2.3. Urine Pregnancy Test At day 1 (prior to randomization), a pregnancy test (urine dipstick) will be done to confirm that women are not pregnant.	7.3.2.3. Urine Pregnancy Test At day 1 (prior to randomization), a pregnancy test (urine dipstick) will be done to confirm that women are not pregnant.	Added a pregnancy test (urine dipstick) at day 1
9. STATISTICS		

Original text with changes shown	New wording	Reason/Justification for change
Section 9.5.4.2		
Supplementary analyses to evaluate effect of assumptions on missing data on the results: • … The resulting complete, imputed datasets will each be analyzed using the same model as the primary analysis model, and the resulting statistics combined using methodology provided by Rubin (1987) and Little and Rubin (2002). • <u>to further alleviate the concern on the uncertainty introduced by missing data, the following 2 separate 1-sided tests of alpha=0.05 with missing data imputed under the corresponding null using a multiple imputation method will be conducted:</u> – <u>in the first test, missing values for the TVB-009P group will be imputed under the non-inferiority null (the lower boundary of the equivalence margin, -1.45%) for testing whether it is non-inferior to PROLIA US;</u> – <u>in the second test, missing values for the TVB-009P group will be imputed under the non-superiority null (+1.45%) for testing whether it is non-superior to PROLIA US.</u> The resulting complete, imputed datasets will each be analyzed using the same model as the primary analysis model, and the resulting statistics combined using methodology provided by Rubin (1987) and Little and Rubin (2002). …	Supplementary analyses to evaluate effect of assumptions on missing data on the results: • … The resulting complete, imputed datasets will each be analyzed using the same model as the primary analysis model, and the resulting statistics combined using methodology provided by Rubin (1987) and Little and Rubin (2002). • to further alleviate the concern on the uncertainty introduced by missing data, the following 2 separate 1-sided tests of alpha=0.05 with missing data imputed under the corresponding null using a multiple imputation method will be conducted: – in the first test, missing values for the TVB-009P group will be imputed under the non-inferiority null (the lower boundary of the equivalence margin, -1.45%) for testing whether it is non-inferior to PROLIA US; – in the second test, missing values for the TVB-009P group will be imputed under the non-superiority null (+1.45%) for testing whether it is non-superior to PROLIA US. The resulting complete, imputed datasets will each be analyzed using the same model as the primary analysis model, and the resulting statistics combined using methodology provided by Rubin (1987) and Little and Rubin (2002). …	Added additional supplementary analyses to further alleviate the concern on the uncertainty introduced by missing data
Appendix A		
Sponsor's Medical Expert/Contact Point designated by the Sponsor for Further Information on the Study **For serious adverse events:** Send by email to the address of the local safety officer/contract research organization (LSO/CRO) provided on the serious	**Sponsor's Medical Expert/Contact Point designated by the Sponsor for Further Information on the Study** **For serious adverse events:** Send by email to the address of the local safety officer/contract research organization (LSO/CRO) provided on the serious	Update

Original text with changes shown	New wording	Reason/Justification for change
adverse event (SAE) report form. ~~In the event of difficulty transmitting the form, contact the email address indicated in the SAE Management Plan (SMP).~~	adverse event (SAE) report form.	
Interactive Voice Recognition System [redacted]	**Interactive Voice Recognition System** [redacted]	Update of contact details

16.2. Local Protocol Amendment 01 for Germany dated 19 May 2021

The primary reason for this local amendment is to implement changes requested by the German Competent Authority.

Original text with changes shown	New wording	Reason/Justification for change
Section 5.8 (last paragraph)		
At the investigational center, only the pharmacist or designee who will dispense the study drug and the study drug administrator will be unblinded. These staff will not participate in <u>any efficacy, pharmacokinetic, pharmacodynamic, immunogenicity, and</u> safety assessments.	At the investigational center, only the pharmacist or designee who will dispense the study drug and the study drug administrator will be unblinded. These staff will not participate in any efficacy, pharmacokinetic, pharmacodynamic, immunogenicity, and safety assessments.	Clarification
Section 7.3.2, other sections affected by this change: Table 1 in Section 3 and Appendix B (visit 1)		
Added new subsection for urine pregnancy test: <u>7.3.2.2. Urine Pregnancy Test</u> <u>At screening, a pregnancy test (urine dipstick) will be done to confirm that women are not pregnant.</u>	7.3.2.2. Urine Pregnancy Test At screening, a pregnancy test (urine dipstick) will be done to confirm that women are not pregnant.	Addition

16.3. Protocol Amendment 01 dated 03 February 2021

The primary reason for this amendment is to update the Legal Representative of the Sponsor in the EU listed in Appendix A. In addition, a few other additions/corrections have been made.

Original text with changes shown	New wording	Reason/Justification for change
Coordinating Investigator Agreement		
[redacted]	[redacted]	Addition
List of Abbreviations and Section 9.5.4.2 Supplementary Analysis for the Primary Analysis		
Missing ~~completely~~ <u>not</u> at random (MNAR)	Missing not at random (MNAR)	Correction

Appendix A, Clinical Laboratories and Other Departments and Institutions		
Legal Representative of the Sponsor in the EU [redacted]	**Legal Representative of the Sponsor in the EU** [redacted]	Update

Appendix A. CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS

Sponsor's Authorized Representative	[redacted]
Legal Representative of the Sponsor in the EU	[redacted]
Sponsor's Medical Expert/Contact Point designated by the Sponsor for Further Information on the Study For serious adverse events: Send by email to the address of the local safety officer/contract research organization (LSO/CRO) provided on the serious adverse event (SAE) report form.	[redacted]
Study Principal Investigator	TBD
Contract Research Organization	[redacted]
Central Clinical Laboratory	[redacted]
Interactive Voice Recognition System	[redacted]
Central Imaging Vendor	[redacted]
Bioanalytical Pharmacokinetics Evaluation,	[redacted]

Bioanalytical Immunogenicity Evaluation, and Pharmacogenomics/Biomarker Evaluation	[redacted]
Randomization and Trial Supply Management (RTSM) vendor	[redacted]

Appendix B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT

Visits 3, 4, 5, 6, 8, 10 and 11 may be conducted at the patient's home should circumstances dictate.

1. **Visit 1: Screening (Up to 4 weeks before Visit 2)**

The screening visit (visit 1) will take place not more than 4 weeks before the baseline visit (visit 2). The following procedures will be performed at visit 1:

- obtain signed and dated informed consent before any study-related procedures are performed
- review inclusion and exclusion criteria
- demographics/medical history
- dispense Vitamin D and calcium supplements
- document prior medication and treatment history
- clinical laboratory test sampling:
  - serum chemistry
  - hematology
  - serum follicle stimulating hormone (FSH) if applicable
  - serum estradiol (E2) if applicable
  - estimated glomerular filtration rate (eGFR) (using the Modification of Diet in Renal Disease [MDRD] formula)
  - serum vitamin D
- physical examination (including height and weight)
- 12-lead electrocardiogram (ECG)
- vital signs measurement
- lumbar spine-bone mineral density assessment (LS-BMD) by dual-energy X-ray absorptiometry (DXA)
- total hip and femoral neck bone mineral density (BMD) assessment by DXA
- lateral spine X-ray
- inquire about adverse events
- inquire about concomitant medications
- inquire about coronavirus disease 2019 (COVID-19)
- COVID-19 viral test (test can be performed any time during the study that the patient displays symptoms)

- inform patients of study restrictions and compliance requirements

2. **Visit 2: Baseline (Day 1)**

Patients who meet the inclusion and exclusion criteria at visit 1 will continue to visit 2, when baseline assessments will be conducted.

The following procedures will be performed at visit 2, prior to investigational medicinal product (IMP) administration:

- review inclusion and exclusion criteria
- pregnancy test (urine dipstick) (prior to randomization)
- assign randomization/treatment numbers and enter in case report form (CRF)
- document prior medication and treatment history
- clinical laboratory test sampling
  - serum chemistry
  - hematology
  - coagulation (international normalized ratio [INR], prothrombin [PT] and partial prothrombin [PPT])
  - cholesterol (low density lipoprotein [LDL], high density lipoprotein [HDL], HDL/total)
  - fasting triglycerides
  - urinalysis
- immunogenicity sampling
  - serum anti-drug antibody (ADA)
- 12-lead ECG
- vital signs measurement
- pharmacokinetics sampling
  - serum concentration of IMP
- pharmacodynamics sampling
  - fasting serum C-telopeptide cross-link of type 1 collagen (sCTX-1) and procollagen type 1 N propeptide (P1NP)
- inquire about adverse events
- inquire about concomitant medications
- inquire about COVID-19
- inform patients of study restrictions and compliance requirements

Patients will have IMP administered by qualified site staff. The following procedure will be performed at visit 2, following IMP administration:

- local tolerability at the injection site
- record device-related adverse events

3. **Visits 3 through 8: Main Treatment Period**

a. Visit 3: Main Treatment Period (Day 15±3 days)

The following procedures will be performed:

- immunogenicity sampling
  - serum ADA
- vital signs measurement
- pharmacokinetics sampling
  - serum concentration of IMP
- pharmacodynamics sampling
  - fasting serum sCTX-1 and P1NP
- inquire about adverse events
- inquire about concomitant medications
- inquire about COVID-19
- inform patients of study restrictions and compliance requirements

b. Visit 4: Main Treatment Period (Week 4±3 days)

The following procedures will be performed:

- clinical laboratory tests sampling
  - serum chemistry
  - hematology
- immunogenicity sampling
  - serum ADA
- vital signs measurement
- pharmacokinetics sampling
  - serum concentration of IMP
- pharmacodynamics sampling
  - fasting serum sCTX-1 and P1NP
- inquire about adverse events
- inquire about concomitant medications

- inquire about COVID-19
- inform patients of study restrictions and compliance requirements

c. Visit 5: Main Treatment Period (Week 8±5 days)

The following procedures will be performed:

- immunogenicity sampling
  - serum ADA
- vital signs measurements
- pharmacokinetics sampling
  - serum concentration of IMP
- pharmacodynamics sampling
  - fasting serum sCTX-1 and P1NP
- inquire about adverse events
- inquire about concomitant medications
- inquire about COVID-19
- inform patients of study restrictions and compliance requirements

d. Visit 6: Main Treatment Period (Week 12±7 days)

The following procedures will be performed:

- clinical laboratory tests:
  - serum chemistry
  - hematology
- immunogenicity sampling
  - serum ADA
- vital signs measurement
- pharmacokinetics sampling
  - serum concentration of IMP
- pharmacodynamics sampling
  - fasting serum sCTX-1 and P1NP
- inquire about adverse events
- inquire about concomitant medications
- inquire about COVID-19
- inform patients of study restrictions and compliance requirements

e. Visit 7: Main Treatment Period (Week 26±7 days)

The following procedures will be performed at visit 7, prior to IMP administration:

- clinical laboratory tests:
  - serum chemistry
  - hematology
  - coagulation (INR, PT and PPT)
  - cholesterol (LDL, HDL, HDL/total)
  - fasting triglycerides
  - urinalysis
- immunogenicity sampling
  - serum ADA
- physical examination (including height and weight)
- 12-lead ECG
- vital signs measurement
- LS-BMD by DXA
- total hip and femoral neck BMD assessment by DXA
- pharmacokinetics sampling
  - serum concentration of IMP
- pharmacodynamics sampling
  - fasting serum sCTX-1 and P1NP
- inquire about adverse events
- inquire about concomitant medications
- inquire about COVID-19
- inform patients of study restrictions and compliance requirements

Patients will have IMP administered by qualified site staff. The following procedure will be performed at visit 7, following IMP administration:

- local tolerability at the injection site
- record device-related adverse events

f. Visit 8: Main Treatment Period (Week 39±14 days)

The following procedures will be performed:

- clinical laboratory tests:
  - serum chemistry

  - hematology
- immunogenicity sampling
  - serum ADA
- vital signs measurements
- pharmacokinetics sampling
  - serum concentration of IMP
- pharmacodynamics sampling
  - fasting serum sCTX-1 and P1NP
- inquire about adverse events
- inquire about concomitant medications
- inquire about COVID-19
- inform patients of study restrictions and compliance requirements

4. **Visit 9: End of Main Treatment Period and Start of Transition Period (Week 52±14 days)**

The following procedures will be performed at visit 9, prior to IMP administration:

- clinical laboratory tests:
  - serum chemistry
  - hematology
  - coagulation (INR, PT and PPT)
  - cholesterol (LDL, HDL, HDL/total)
  - fasting triglycerides
  - urinalysis
- immunogenicity sampling
  - serum ADA
- physical examination (including height and weight)
- 12-lead ECG
- vital signs measurement
- LS-BMD by DXA
- Total hip and femoral neck BMD by DXA
- lateral spine X-ray
- pharmacokinetics sampling
  - serum concentration of IMP

- pharmacodynamics sampling
  - fasting serum sCTX-1 and P1NP
- inquire about adverse events
- inquire about concomitant medications
- inquire about COVID-19
- inform patients of study restrictions and compliance requirements
- randomization for the transition period. Patients in the PROLIA US treatment group will be re-randomized in a 1:1 ratio to receive a third dose of PROLIA US or switch to TVB-009P and receive a single dose of TVB-009P in the transition period. Patients who were initially randomized to TVB-009P will continue to receive TVB-009P; however, to maintain blinding, the randomization process will be performed for all patients (although only patients in the PROLIA US arm will actually be re-randomized). Randomization will not be applied to patients where this visit is for early termination.

Patients will have IMP administered by qualified site staff. The following procedure will be performed at visit 9, following IMP administration:

- local tolerability at the injection site
- record device-related adverse events

5. **Visit 10: Transition Period (Week 54, 2 weeks±3 days after Visit 9)**

The following procedures will be performed:

- immunogenicity sampling
  - serum ADA
- vital signs measurement
- pharmacokinetics sampling
  - serum concentration of IMP
- pharmacodynamics sampling
  - fasting serum sCTX-1 and P1NP
- inquire about adverse events
- inquire about concomitant medications
- inquire about COVID-19
- inform patients of study restrictions and compliance requirements

6. **Visit 11: Transition Period (Week 65, 13 weeks±14 days after Visit 9)**

The following procedures will be performed:

- clinical laboratory tests:

  - serum chemistry
  - hematology
- immunogenicity sampling
  - serum ADA
- vital signs measurement
- pharmacokinetics sampling
  - serum concentration of IMP
- pharmacodynamics sampling
  - fasting serum sCTX-1 and P1NP
- inquire about adverse events
- inquire about concomitant medications
- inquire about COVID-19
- inform patients of study restrictions and compliance requirements

7. **Visit 12: End of Study/Early Termination (Week 78, 26 weeks±14 days after Visit 9)**

The following procedures will be performed:

- clinical laboratory tests:
  - serum chemistry
  - hematology
- immunogenicity sampling
  - serum ADA
- physical examination (including height and weight)
- 12-lead ECG
- vital signs measurement
- total hip and femoral neck BMD assessment by DXA (assessment will not be performed for patients where this visit is for early termination, unless early termination occurs between the week 26 and week 52 visits [the minimum time between two DXA scans should be 3 months])
- lateral spine X-ray (assessment will not be performed for patients where this visit is for early termination, unless early termination occurs between the week 26 and week 52 visits)
- LS-BMD by DXA (assessment will not be performed for patients where this visit is for early termination, unless early termination occurs between the week 26 and week 52 visits [the minimum time between two DXA scans should be 3 months])

- pharmacokinetics sampling
  - serum concentration of IMP
- pharmacodynamics sampling
  - fasting serum sCTX-1 and P1NP
- inquire about adverse events
- inquire about concomitant medications
- inquire about COVID-19

8. Unscheduled Visits

An unscheduled visit may be performed at any time during the study at the patient's request and as deemed necessary by the investigator. The date and reason for the unscheduled visit will be recorded on the CRF as well as any other data obtained from procedures and assessments.

Procedures performed during unscheduled visits include:

- vital signs measurement
- inquire about adverse events
- inquire about concomitant medication
- inquire about COVID-19
- inform patients of study restrictions and compliance requirements

Other procedures and assessments may be performed at the discretion of the investigator.

APPENDIX C. QUALITY CONTROL AND QUALITY ASSURANCE

Protocol Amendments and Protocol Deviations

Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the Independent Ethics Committee (IEC)/ Institutional Review Board (IRB) and national and local competent authorities, as applicable, except when necessary to address immediate safety concerns to the patients or when the change involves only logistics or administration. The principal investigator at each investigational center, the coordinating investigator (if applicable), and the sponsor will sign the protocol amendment.

Important Protocol Deviations

Any deviation from the protocol that affects, to a significant degree, (a) the safety, physical, or mental integrity of the patients in the study and/or (b) the scientific value of the study will be considered an important protocol deviation. Important protocol deviations may include non-adherence on the part of the patient, the investigator, or the sponsor to protocol-specific inclusion and exclusion criteria, primary objective variable criteria, or good clinical practice (GCP) guidelines; noncompliance to investigational medicinal product (IMP) administration; use of prohibited medications. Important protocol deviations will be identified and recorded by investigational center personnel. All important protocol deviations will be reported to the responsible IEC/IRB, as required.

When an important protocol deviation is reported, the sponsor will determine whether to withdraw the patient from the study or permit the patient to continue in the study, with documented approval from the medical expert. The decision will be based on ensuring the safety of the patient and preserving the integrity of the study.

If a patient experiences an adverse event or medical emergency, deviations from the protocol may be allowed on a case-by-case basis. To ensure patient safety, after the event has stabilized or treatment has been administered (or both), the investigator or other physician in attendance must contact the physician identified in the Clinical Study Personnel Contact Information section of this protocol as soon as possible to discuss the situation. The investigator, in consultation with the sponsor, will decide whether the patient should continue to participate in the study.

Changes in the inclusion and exclusion criteria of the protocol are **not** prospectively granted by the sponsor. If investigational center personnel learn that a patient who did not meet protocol inclusion and exclusion criteria was entered in a study, they must immediately inform the sponsor of the important protocol deviation. If such patient has already completed the study or has withdrawn early, no action will be taken but the deviation will be recorded.

Information to Study Personnel

The investigator is responsible for giving information about the study to all personnel members involved in the study or in any element of patient management, both before starting the study and during the course of the study (eg, when new personnel become involved). The investigator must ensure that all study personnel are qualified by education, experience, and training to perform

their specific task. These study personnel members must be listed on the investigational center authorization form, which includes a clear description of each personnel member's responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study personnel, including the investigator, and for ensuring they comply with the protocol.

Study Monitoring

To ensure compliance with GCP guidelines, the study monitor or representative is responsible for ensuring that patients have signed the informed consent form (ICF) and the study is conducted according to applicable SOPs, the protocol, and other written instructions and regulatory guidelines.

The study monitor is the primary association between the sponsor and the investigator. The main responsibilities of the study monitor are to visit the investigator before, during, and after the study to ensure adherence to the protocol, that all data are correctly and completely recorded and reported, and that informed consent is obtained and recorded for all patients before they participate in the study and when changes to the consent form are warranted, in accordance with IEC/IRB approvals.

The study monitor will contact the investigator and visit the investigational center according to the monitoring plan. The study monitor will be permitted to review and verify the various records (case report forms [CRF]s and other pertinent source data records, including specific electronic source document relating to the study) to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded.

As part of the supervision of study progress, other sponsor personnel may, on request, accompany the study monitor on visits to the investigational center. The investigator and assisting personnel must agree to cooperate with the study monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected during the course of these monitoring visits or provided in follow-up written communication.

For COVID-19 updates, refer to Appendix M.

Audit and Inspection

The sponsor may audit the investigational center to evaluate study conduct and compliance with protocols, standard operating procedures (SOP)s, GCP guidelines, and applicable regulatory requirements. The sponsor's Global Clinical Quality Assurance, independent of Global Specialty Development, is responsible for determining the need for (and timing of) an investigational center audit.

The investigator must accept that competent authorities and sponsor representatives may conduct inspections and audits to verify compliance with GCP guidelines.

For COVID-19 updates, refer to Appendix M.

APPENDIX D. ETHICS

Informed Consent

The investigator, or a qualified person designated by the investigator, should fully inform the patient of all pertinent aspects of the study, including the written information approved by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB). All written and oral information about the study will be provided in a language as nontechnical as practical to be understood by the patient. The patient should be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. The above should be detailed in the source documents.

Written informed consent will be obtained from each patient before any study specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. The patient's willingness to participate in the study will be documented in the informed consent form (ICF), which will be signed and personally dated by the patient and by the person who conducted the informed consent discussion. The investigator will keep the original informed consent forms, and copies will be given to the patients. It will also be explained to the patients that the patient is free to refuse participation in the study and free to withdraw from the study at any time without prejudice to future treatment.

Adult patients with a legally acceptable representative should provide informed consent according to national and local requirements.

Competent Authorities and Independent Ethics Committees/Institutional Review Boards

Before this study starts, the protocol will be submitted to the national competent authority and to the respective IEC/IRB for review. As required, the study will not start at a given investigational center before the IEC/IRB and competent authority (as applicable) for the investigational center give written approval or a favorable opinion.

Confidentiality Regarding Study Patients

The investigator must ensure that the privacy of the patients, including their identity and all personal medical information, will be maintained at all times. In case report forms (CRF)s and other documents or image material submitted to the sponsor, patients will be identified not by their names, but by an identification number.

Personal medical information may be reviewed for the purpose of patient safety or for verifying data in the source and the CRF. This review may be conducted by the study monitor, properly authorized persons on behalf of the sponsor, Global Quality Assurance (GCA), or competent authorities. Personal medical information will always be treated as confidential.

Registration of the Clinical Study

In compliance with national and local regulations and in accordance with Teva standard procedures, this clinical study will be registered on trials registry websites.

APPENDIX E. LOST TO FOLLOW-UP

A patient will be considered lost to follow-up if she repeatedly fails to return for scheduled visits and is unable to be contacted by the investigational center.

The following actions must be taken if a patient fails to return to the investigational center for a required study visit:

- The investigational center must attempt to contact the patient and reschedule the missed visit as soon as possible, counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- In cases in which the patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, she will be considered to have withdrawn from the study with a primary reason of 'lost to follow-up'.

Appendix F. LIST OF PROHIBITED MEDICATIONS

Any osteoporosis treatment (other than calcium and vitamin D supplements) or ongoing use of any bone active drugs are prohibited during study.

- denosumab, other than the study drug
- romosozumab
- strontium
- fluoride (for treatment of osteoporosis)
- intravenous (iv) bisphosphonates
- oral bisphosphonates
- teriparatide or any parathyroid hormone (PTH) analogs
- tibolone or any systemic oral or transdermal estrogen or selective estrogen receptor modulators (SERM)s
- calcitonin
- cinacalcet
- prolonged (ie, >2 months) systemic glucocorticoid therapy
- heparin (except topical)
- anti-convulsives (with the exception of benzodiazepines)
- systemic ketoconazole
- adrenocorticotropic hormone
- lithium
- gonadotropin releasing hormone agonists, or anabolic steroids

APPENDIX G. CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS

As detailed by Sampson et al 2006, anaphylaxis is broadly defined as, "a serious allergic reaction that is rapid in onset and may cause death." Diagnostic criteria defined by the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network during the second symposium on the definition and management of anaphylaxis, modified from Sampson et al 2006, are as follows:

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue, uvula) and at least 1 of the following:
   - respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
   - reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen* for that patient (minutes to several hours):
   - involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   - respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   - reduced blood pressure (BP) or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   - persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure *to a known allergen* for that patient (minutes to several hours):
   - adults: systolic BP of <90 mm Hg or >30% decrease from that person's baseline

In the event of suspected severe hypersensitivity (including anaphylaxis), vital signs, including oxygen saturation and respiration rate, will be measured. Other assessments will be performed at the discretion of the investigator.

APPENDIX H. PRODUCT COMPLAINTS

1. Clinical Product Complaints/Device Deficiency

A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical investigational medicinal product (IMP) supplies or clinical device supplies used in a clinical research study sponsored by Teva. Examples of a product complaint include but are not limited to:

- suspected contamination
- questionable stability (eg, color change, flaking, crumbling, etc.)
- defective components
- missing or extra units (eg, primary container is received at the investigational center with more or less than the designated number of units inside)
- incorrect packaging, or incorrect or missing labeling/labels
- device not working correctly or appears defective in some manner

Each investigational center will be responsible for reporting a possible clinical product complaint/device deficiency by completing the product complaint form provided by Teva and emailing it to clinical.productcomplaints@tevapharm.com within 48 hours of becoming aware of the issue.

For complaints involving a device, combination product (CP) or other retrievable item, it is required that the device/CP (or item) be sent back to the sponsor for investigative testing whenever possible. For complaints involving an IMP, all relevant samples (eg, the remainder of the patient's IMP supply) should be sent back to the sponsor for investigative testing whenever possible.

Product Complaint Information Needed from the Investigational Center

In the event that the product complaint form cannot be completed, the investigator will provide the following information, as available:

- investigational center number and principal investigator name
- name, phone number, and address of the source of the complaint
- clinical protocol number
- patient identifier (patient study number) and corresponding visit numbers, if applicable
- patient number for double-blind studies
- product available for return: Yes/No
- product was taken or used according to protocol: Yes/No
- description or nature of complaint
- associated serious adverse event or serious adverse device event: Yes/No

- device deficiency that could lead to a serious adverse event: Yes/No
- clinical supplies unblinded (for blinded studies): Yes/No
- date and name of person receiving the complaint

Note: Reporting a product complaint/device deficiency must not be delayed even if not all the required information can be obtained immediately. Known information must be reported immediately. The sponsor will collaborate with the investigator to obtain any outstanding information.

Handling of Investigational Medicinal Product(s) and Devices at the Investigational Center(s)

The investigator is responsible for retaining the product or device in question in a location separate from the investigator's clinical study supplies. The sponsor may request that the investigator return the product for further evaluation and/or analysis. If this is necessary, the clinical study monitor or designee will provide the information needed for returning the IMP/device.

If it is determined that the investigational center must return all IMP/devices, the sponsor will provide the information needed to handle the return.

The integrity of the randomization code and corresponding blinded clinical supplies will be maintained whenever possible. A serious adverse event or the potential for a product quality problem existing beyond the scope of the complaint may be a reason to unblind the clinical supplies for an affected patient.

Adverse Events or Serious Adverse Events Associated with a Product Complaint

If there is an adverse event or serious adverse event due to product complaint, the protocol should be followed for recording and reporting (Section 7.1.2 and Section 7.1.5.3, respectively).

Documenting a Product Complaint

The investigator will record in the source documentation a description of the product complaint, the initial determination if the deficiency could have led to a serious adverse event, and any actions taken to resolve the complaint and to preserve the safety of the patient. Once the complaint has been investigated by the sponsor and the investigator, if necessary, an event closure letter may be sent to the investigational center where the complaint originated or to all investigational centers using the product or device.

Medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study.

1. Assessment of Device Performance

Device performance will be assessed by device deficiencies and product complaints.

A device deficiency is any inadequacy of an investigational medical device with respect to its identity, quality, durability, reliability, safety, or performance that has not led to an adverse event (Figure 3). This definition includes malfunctions, use errors, inadequate labeling (eg, unintelligible label, incorrect expiry date).

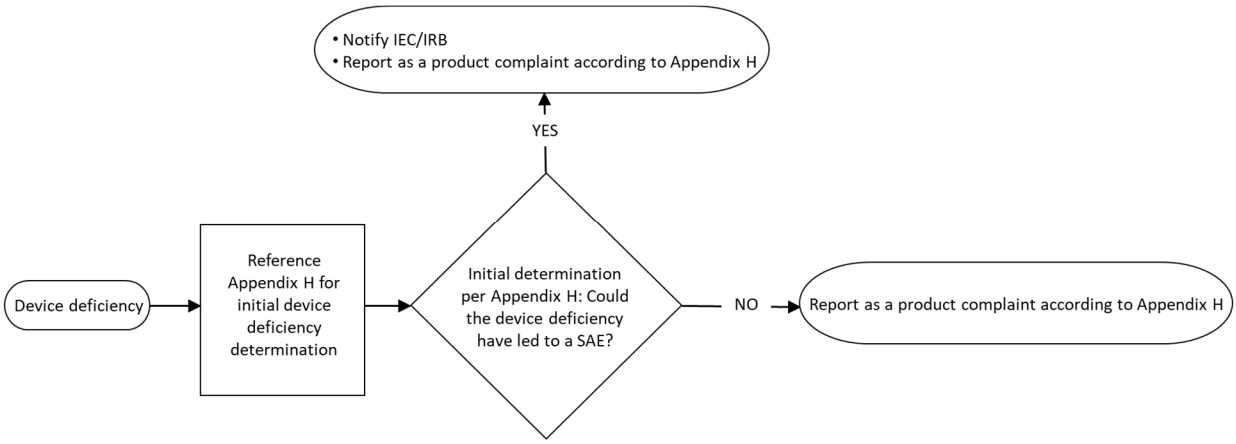
The investigator should try to determine whether the device deficiency could have led to a serious adverse event and include this assessment in the product complaint form.

Device deficiencies with potential serious adverse device effect are deficiencies that might have led to a serious adverse device effect if:

- suitable action had not been taken (or)
- intervention had not been made (or)
- if circumstances had been less fortunate

These device deficiencies shall be reported to the IEC/IRB by the investigator and to the regulatory authorities by the sponsor according to the national and local regulations.

Figure 3: Decision Tree for Device Deficiencies



IEC=Institutional ethics committee; IRB=Institutional Review Board; SAE=serious adverse event.

APPENDIX I. PHARMACOKINETICS AND PHARMACODYNAMICS

Specimen Sampling and Handling

For serum collection, samples will be collected in vacutainer tubes containing no anticoagulant and allowed to set at room temperature for between 1 and 1.5 hours to allow for serum separation to occur. Samples will then be centrifuged (1500g, approximately 10 minutes, at 4 to 8°C). Separated serum will be transferred in approximately equal portions into 2 opaque, labeled, polypropylene tubes (Sets A and B).

Labels for samples should include study number, patient randomization number, period, nominal collection time, Set A or B, and indication that they are pharmacokinetic/pharmacodynamic samples. Samples will be stored at a temperature -80°C (nominal) in an upright position until they are shipped to the bioanalytical laboratory ([redacted]) for analysis.

Shipment and Analysis of Samples

Serum samples for all patients will be shipped from the investigational center to the GBT, in dry ice with temperature data logger. The bioanalytical laboratory ([redacted]) will be notified before the shipment of the samples and the shipping information will be sent when the samples are shipped. An electronic file containing sample demographics will be emailed to the bioanalytical laboratory and the sponsor's representatives from bioanalytical departments for each shipment.

Set A samples will be transported with a temperature data logger and frozen with dry ice sufficient for 4 days, by next-day courier to the bioanalytical laboratory ([redacted]).

Set B samples will be sent to the same laboratory as that for Set A samples on a subsequent day by next-day courier. Instructions as to the disposition of the Set B samples will be provided by the sponsor.

Samples should not be shipped on a holiday. Samples are not to arrive on the [redacted] weekend or a holiday.

Samples will be analyzed using an appropriate validated method. Timing of the initiation of sample analysis will be determined by the sponsor's representatives of bioanalytical departments responsible for the bioanalysis while keeping the study blinding intact.

APPENDIX J. IMMUNOGENICITY SAMPLES

Blood Sampling and Handling

For serum collection, samples will be collected in vacutainer tubes containing no anticoagulant, and allowed to set at room temperature for between 1 and 1.5 hours to allow for serum separation to occur. Samples will then be centrifuged (1500g, approximately 10 minutes, at 4 to 8°C). Separated serum will be transferred in approximately equal portions into 2 opaque, labeled, polypropylene tubes (Sets A and B).

Label of samples should include study number, patient randomization number, period, nominal collection time, Set A or B, and indication that they are anti-drug antibodies (ADA) samples. Serum samples will be stored at a temperature of -80°C (nominal) in an upright position until they are shipped to the bioanalytical laboratory [redacted]

Shipment and Analysis of Samples

Serum samples for all patients will be shipped from the investigational center to the bioanalytical laboratory ([redacted]), in dry ice with a temperature data logger. The bioanalytical laboratory ([redacted]) will be notified before the shipment of the samples and the shipping information will be sent when the samples are shipped. An electronic file containing sample demographics will be emailed to the bioanalytical laboratory and the sponsor's representatives from bioanalytical departments for each shipment.

Set A samples will be transported with a temperature data logger and frozen with dry ice sufficient for 4 days, by next-day courier to the bioanalytical laboratory [redacted]).

Set B samples will be sent to the same laboratory as that for Set A samples on a subsequent day by next-day courier. Instructions as to the disposition of the Set B samples will be provided by the sponsor.

Samples should not be shipped on a holiday. Samples are not to arrive on the [redacted] weekend or a holiday.

Samples will be analyzed using an appropriate validated method. Timing of the initiation of sample analysis will be determined by the sponsor's representatives of bioanalytical departments responsible for the bioanalysis while keeping the study blinding, if any, intact.

APPENDIX K. DATA MANAGEMENT AND RECORD KEEPING

Direct Access to Source Data and Documents

All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the case report form (CRF). Data may not be recorded directly on the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the CRF.

If data are processed from other institutions or by other means (eg, clinical laboratory, central image center, or electronic diary data) the results will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management).

The medical experts, study monitors, auditors, Independent Ethics Committee (IEC)/Institutional Review Board (IRB), and inspectors from competent authority (or their agents) will be given direct access to source data and documents (eg, medical charts/records, laboratory test results, printouts, videotapes) for source data verification, provided that patient confidentiality is maintained in accordance with national and local requirements.

The investigator must maintain the original records (ie, source documents) of each patient's data at all times. The investigator must maintain a confidential patient identification list that allows the unambiguous identification of each patient.

Data Collection

Data will be collected using CRFs that are specifically designed for this study. The data collected on the CRFs will be captured in a clinical data management system (CDMS) that meets the technical requirements described in 21 Code of Federal Regulations (CFR) Part 11 (United States of America) and documents of other concerned competent authorities. Before using the CDMS, it will be fully validated and all users will receive training on the system and study-specific training. After they are trained, users will be provided with individual system access rights.

Data will be collected at the investigational center by appropriately designated and trained personnel, and CRFs must be completed for each patient who provided informed consent. Patient identity should not be discernible from the data provided on the CRF.

If data are processed from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary data, electronic patient-reported outcome tablet), these data will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management). All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the CRF. Data may not be recorded directly on the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the CRF.

For patients who enter a study but do not meet entry criteria, at a minimum, data for screening failure reason, demography, and adverse events from the time of informed consent will be entered in the CRF.

Data Quality Control

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Oversight will be carried out as described in the sponsor's standard operating procedures (SOP)s for clinical studies. Day to day data management tasks for this study are delegated to a contract organization, and these functions may be carried out as described in the SOPs for clinical studies at that organization. These SOPs will be reviewed by the sponsor before the start of data management activities.

Data will be verified by the study monitor using the data source, and reviewed by data management using both automated logical checks and manual review. Data identified as erroneous, or data that are missing, will be referred to the investigational center for resolution through data queries. Any necessary changes will be made in the clinical database, and data review and validation procedures will be repeated as needed. Data from external sources will be compared with the information available in the CDMS and any discrepancies will be queried.

Applicable terms will be coded according to the coding conventions for this study.

At the conclusion of the study, the CDMS and all other study data will be locked to further additions or corrections. Locking the study data represents the acknowledgment that all data have been captured and confirmed as accurate. All data collected will be approved by the investigator at the investigational center. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate.

Archiving of Case Report Forms and Source Documents

Sponsor Responsibilities

The original CRFs will be archived by the sponsor. Investigational center-specific CRFs will be provided to the respective investigational centers for archiving.

Investigator Responsibilities

The investigator must maintain all written and electronic records, accounts, notes, reports, and data related to the study and any additional records required to be maintained under country, state/province, or national and local laws, including, but not limited to:

- full case histories
- signed informed consent forms (ICF)s
- patient identification lists
- CRFs for each patient on a per-visit basis
- data from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary)
- safety reports
- financial disclosure reports/forms

- reports of receipt, use, and disposition of the investigational medicinal product (IMP)s
- copies of all correspondence with sponsor, the Independent Ethics Committee (IEC)/Institutional Review Board (IRB), and any competent authority

The investigator will retain all records related to the study and any additional records required, as indicated by the protocol and according to applicable laws and regulations, until the Clinical Research Organization (CRO) or sponsor notifies the institution in writing that records may be destroyed. If, after 25 years from study completion, or earlier in the case of the investigational center closing or going out of business, the investigator reasonably determines that study record retention has become unduly burdensome, and sponsor has not provided written notification of destruction, then the investigator may submit a written request to sponsor at least 60 days before any planned disposition of study records. After receipt of such request, the sponsor may make arrangements for appropriate archival or disposition, including requiring that the investigator deliver such records to the sponsor. The investigator shall notify the sponsor of any accidental loss or destruction of study records.

APPENDIX L. PUBLICATION POLICY

All unpublished information given to the investigator by the sponsor shall not be published or disclosed to a third party without the prior written consent of the sponsor.

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

The sponsor will comply with the requirements for publication of study results: "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" (International Committee of Medical Journal Editors [ICMJE] 2019). Publication of the results will occur in a timely manner according to applicable regulations. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual investigational center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements:

- substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work
- drafting the work or revising it critically for important intellectual content
- final approval of the version to be published
- agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

The publications committee established by the sponsor will oversee this process. Additional publications may follow. Policies regarding the publication of the study results are defined in the financial agreement.

No patent applications based on the results of the study may be made by the investigator nor may assistance be given to any third party to make such an application without the written authorization of the sponsor.

APPENDIX M. MANAGEMENT OF STUDY ACTIVITIES DURING COVID-19 OUTBREAKS

This appendix is to address the modifications to the protocol that will be effective during Coronavirus Disease 2019 (COVID-19) outbreaks that affect the conduct of the study. When the situation at specific sites/countries allows the return to regular study activities, this appendix will be void for those sites/countries.

Section 3.1. General Study Design and Study Schematic Diagram; Section 3.5. Schedule of Study Procedures and Assessments

In the event of an emergency situation (eg, COVID-19 outbreaks), in case a patient cannot return to the clinic for the scheduled visits (eg, due to quarantine, isolation, patient's concern, active COVID-19 infection, or closure of the site clinic) remote assessment of safety via telephone and/or videoconference (VC), with VC being the preferred method, may be allowed.

Modifications to other procedures and assessments, electrocardiogram (ECG), laboratory sample collection (including pharmacokinetics, immunogenicity, and pharmacodynamics, etc.) might be performed per implemented contingency measures according to sponsor instructions and the corresponding manual. For example, if central laboratory samples cannot be collected for safety assessments, sites may have patients visit a local reference laboratory or dispatch a home health nurse to perform the assessments, but only after consultation with the sponsor, see Sections 7 and Section 8 below for details.

If pharmacokinetics, immunogenicity, and pharmacodynamics cannot be collected at site, sites may use a home health nurse to collect these blood samples, but only after consultation with the sponsor, see Sections 7 and Sections 7.4-7.8 below for details. The same collection process and equipment will be used in these circumstances.

For dual-energy X-ray absorptiometry (DXA) and X-ray procedures, see Section 6 below.

In addition, the investigational medicinal product (IMP) may be administered according to the schedule outlined in the protocol by blinded study personnel, or home care service providers trained according to study specifications, via visits to the patient's place of residence. The patient's consent to the home visit will be collected in advance. The IMP will be transported, prepared, and administered in a blinded fashion per the conditions specified in the pharmacy manual and the injection instructions.

If the patient does not continue in the study due to site closure, the patient status should be NOT COMPLETED DUE TO: Other COVID-19 logistical reasons prevented patient's continuation in the study.

These measures will be implemented on a case-by-case basis, and only when and where they are warranted due to the emergency situation. Preferably, the original protocol instructions will be followed whenever the new instructions are not required.

Section 4.3.Withdrawal Criteria and Procedures for the Patient

If a patient exhibits clinical symptoms that may indicate COVID-19 infection after entering the study, the patient should be tested for active COVID-19. If the patient tests positive for active

COVID-19, she may continue for scheduled visits when recovered (ie, tests negative for active COVID-19).

Section 6. Assessment of Efficacy

In the event of an emergency situation (eg, COVID-19 outbreaks), in case a patient cannot return to the clinic/site for the scheduled visits (eg, due to quarantine, isolation, patient's concern, active COVID-19 infection, or closure of the site clinic), DXA and X-ray procedures should be performed if the responsible location is not affected by the restrictions. If the responsible location used for DXA and X-ray cannot be visited due to special circumstances it should be evaluated if another location might be used after consultation and approval by the sponsor.

These measures will be implemented on a case-by-case basis, and only when and where they are warranted due to the emergency situation. Preferably, the full protocol instructions will be followed whenever the modified instructions are not required.

Section 7. Assessment of Safety

In the event of an emergency situation (eg, COVID-19 outbreaks), in case a patient cannot return to the clinic for the scheduled visits (eg, due to quarantine, isolation, patient's concern, active COVID-19 infection, or closure of the site clinic), remote assessment of safety (as well as inquiries regarding adverse events and use of concomitant medication) via telephone call and/or VC, with VC being the preferred method, may be allowed. The results will be directly entered into the case report form (CRF) per the usual process.

Modifications to other procedures and assessments (ECG, laboratory sample collection, etc.) might be performed per implemented contingency measures according to sponsor instructions. For example, if central laboratory samples cannot be collected for safety assessments, sites may have patients visit a local reference laboratory or dispatch a home health nurse to perform the assessments, but only after consultation with the sponsor.

These measures will be implemented on a case-by-case basis, and only when and where they are warranted due to the emergency situation. These measures will not be implemented for patients known to be COVID-19 positive. Preferably, the original protocol instructions will be followed unless the instructions in this appendix are implemented by the sponsor.

Section 7.3. Clinical Laboratory Tests

If central laboratory samples cannot be collected for safety assessments sites may have patients visit a local reference laboratory or arrange a home health visit to perform the assessments after discussion with and approval by the sponsor. If any patient has clinical laboratory samples collected at a local laboratory, the site will be responsible for collection of reference ranges from that laboratory.

Section 7.4. Physical Examinations; Section 7.5. Vital Signs; Section 7.6. Electrocardiography; Section 7.7. Assessment of Local Tolerability and Pain

At-home health visits may be used to perform safety assessments such as physical examinations, vital signs, ECG, and local tolerability to determine any new adverse events.

Section 8. Assessments of Pharmacokinetics and Immunogenicity; Section 6.2. Pharmacodynamics Assessment

If pharmacokinetic, pharmacodynamic, and immunogenicity samples cannot be collected due to limitations in ability to carry out the procedure or limitations in storage and shipments, the samples will not be collected for those respective visits. Study samples collected from confirmed COVID-19 positive patients during the study, with confirmation either before or after the sample collection, will be kept at the central laboratory and will not be shipped to Teva bioanalytical laboratories nor analyzed. Teva bioanalytical laboratories will be informed within approximately 1 week of any COVID-19 positive patients confirmed after samples being collected.

Section 10. Quality Control and Quality Assurance; Appendix C. Quality Control and Quality Assurance

Deviations from the study conduct due to emergency situations (eg, COVID-19 outbreaks), including implemented contingency measures and their impact (eg, patient discontinuation from the study, alternative procedures used to collect critical safety and/or efficacy data, etc.), will be described in the appropriate sections of the clinical study report (CSR).