NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY (PASS) PROTOCOL

EUROPEAN NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY TO EVALUATE CARDIOVASCULAR EVENTS AND ALL-CAUSE MORTALITY IN PATIENTS NEWLY EXPOSED TO ABALOPARATIDE OR TERIPARATIDE

Non-interventional PASS Protocol - original	08 March 2023
Non-interventional PASS Protocol – Version 2.0	29 September 2023
Non-interventional PASS Protocol – Version 3.0	20 February 2024
Non-interventional PASS Protocol – Version 4.0	20 June 2025
Non-interventional PASS Protocol – Version 5.0	16 October 2025
Non-interventional PASS Protocol – Version 6.0	23 February 2026
Non-interventional PASS Protocol – Version 7.0	14 July 2026

PASS INFORMATION

Title	European non-interventional post-authorization safety study (PASS) to evaluate cardiovascular (CV) events and all-cause mortality in patients newly exposed to abaloparatide or teriparatide.
Protocol number	1.0
Version number	7.0
Date of last version of protocol	23 February 2026
EU PAS register number:	EUPAS1000000613
Procedure number:	EMEA/H/C/005928/0000
Marketing Authorisation Holder (MAH) of Eladynos	Theramex Ireland Ltd.
Phase of development	IV, non-interventional study
Active substance	Abaloparatide (ATC code: H05AA04) Teriparatide (ATC code: H05AA02)
Medicinal product(s)	Eladynos Teriparatide products
Indication	Treatment of osteoporosis in postmenopausal women at increased risk of fracture
Research question and objectives	Abaloparatide is associated with transient increases in heart rate. These transient increases in heart rate were not associated with an increased number of major adverse cardiovascular (CV) events (MACE) or arrhythmias, neither in the clinical developmental program, nor in the retrospective observational cohort study (BA058-05-028), nor from the five and half years of post-marketing experience in the United States. Due to the transient increase in heart rate associated with abaloparatide, CV events of myocardial infarction (MI), stroke and arrhythmia are identified as potential safety risks in the European Union (EU)-Risk Management Plan (RMP) for abaloparatide. This PASS is being conducted to further quantify the potential risk of serious CV events and arrhythmias with abaloparatide in comparison to teriparatide in routine clinical practice in patients.

	Research Question: Is the risk of major cardiovascular events (MACE-1 and MACE-2), arrhythmia, and all-cause mortality (including CV death) associated with abaloparatide use in women in routine clinical practice not different relative to teriparatide? The primary objective of this study is to evaluate the risk of major CV events of MACE-1 (defined as events of MI, stroke, or CV death) potentially associated with the use of abaloparatide, in comparison with the use of teriparatide in routine clinical practice. The secondary objectives of this study are to evaluate the risk of MACE-2 (defined as events of MI, stroke, or all-cause mortality including CV death), MI, stroke, CV death, all-cause mortality, and arrhythmia potentially associated with the use of abaloparatide in comparison with the use of teriparatide in routine clinical practice.
Countries of study	Spain, Germany, and UK
Authors	Maria T Sanchez-Santos, Nicola Barclay, Eng Hooi (Cheryl) Tan, Trishna Rathod-Mistry and Daniel Prieto-Alhambra

MARKETING AUTHORIZATION HOLDER

Marketing authorization holder (MAH) of Eladynos	Theramex Ireland Ltd, 3rd Floor, Kilmore House Park Lane, Spencer Dock Dublin 1, D01 YE64 Ireland
MAH of Eladynos contact person	Senior Director Pharmacovigilance

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2 LIST OF ABBREVIATIONS

Abbreviation	Definition
ABL	Abaloparatide
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CDM	Common data model
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
CV	Cardiovascular
EMA	European Medicines Agency
EMR	Electronic medical record
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GP	General practitioner
HR	Hazard ratio
ICD-9-CM	International Classification of Diseases, revision 9, clinical modification
ICD-10	International Classification of Diseases, revision 10
IR	Incidence rate
LDL	Low-density lipoprotein
LPD	Longitudinal Patient Database
MACE	Major adverse cardiac event(s)
MAH	Marketing Authorization Holder
MI	Myocardial infarction
OHDSI	Observational health data sciences and informatics
OMOP	Observational medical outcomes partnership
OP	Osteoporosis
PASS	Post-authorization safety study(ies)
PY	Person-years
PMSI	Programme de médicalisation des systèmes d`information
PS	Propensity score(s)
PV	Pharmacovigilance
RMP	Risk Management Plan

Abbreviation	Definition
SAP	Statistical Analysis Plan
SD	Standard deviation
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
SmPC	Summary of Product Characteristics
TPTD	Teriparatide
WHO	World Health Organization

3 RESPONSIBLE PARTIES

Function	Name	Title	Affiliation	Address
Study Coordinator (UK)	Trishna Rathod-Mistry	Senior researcher in epidemiology and medical statistics	The Chancellor, Masters, and Scholars of the University of Oxford	Wellington Square, Oxford, OX1
Study Coordinator (UK)	Daniel Prieto Alhambra	Professor of Pharmaco- and Device Epidemiology	The Chancellor, Masters, and Scholars of the University of Oxford	Wellington Square, Oxford, OX1
Study Manager (UK)	Mahkameh Mafi	Personal Assistant and Senior Administrator for Health Data Sciences	The Chancellor, Masters, and Scholars of the University of Oxford	Wellington Square, Oxford, OX1
Senior Epidemiologist (UK)	Eng Hooi (Cheryl) Tan	Senior researcher in pharmacoepidemiology	The Chancellor, Masters, and Scholars of the University of Oxford	Wellington Square, Oxford, OX1
Data scientist (UK)	Mike Du	Postdoctoral data scientist	The Chancellor, Masters, and Scholars of the University of Oxford	Wellington Square, Oxford, OX1

Function	Name	Title	Affiliation	Address
EU and Global Regulatory Lead - Contact Person (MAH)		Senior Director Regulatory Affairs	Theramex HQ UK Ltd	50 Broadway, London, SW1H 0BL, UK
Real World Evidence Lead Scientist - Contact Person (MAH)		Senior Manager - Global Medical affairs– Osteoporosis	Theramex HQ UK Ltd	50 Broadway, London, SW1H 0BL, UK
Safety Lead Abaloparatide - Contact Person (MAH)		Senior Director Pharmacovigilance	Theramex HQ UK Ltd	50 Broadway, London, SW1H 0BL, UK
Participating countries				
Data source SIDIAP (ES)		Dr. (MPH, PhD)	Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol)	Gran Via de les Corts Catalanes, 587, 08007 àtic, Barcelona, Spain
Data source IQVIA Germany DA (DE)		Principal of Data Standardization & Analytics	IQVIA	IQVIA Inc., 100 IMS Drive, Parsippany NJ 07054
Data source CPRD Aurum (UK)		Senior Researcher (OMOP)	Clinical Practice Research Datalink (CPRD) Medicines and Healthcare products Regulatory Agency	10 South Colonnade, Canary Wharf, London E14 4PU, United Kingdom
Data source IQVIA PharMetrics® Plus (US)		Principal of Data Standardization & Analytics	IQVIA	IQVIA Inc., 100 IMS Drive, Parsippany NJ 07054

DA=Disease Analyzer; DE=Germany; ES=Spain; EU=European Union; MAH=Marketing Authorization Holder; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària

4 ABSTRACT

Title: European non-interventional post-authorization safety study (PASS) to evaluate cardiovascular (CV) events in patients newly exposed to abaloparatide or teriparatide.

Rationale and background

Abaloparatide is associated with transient increases in heart rate. These transient increases in heart rate were not associated with an increased number of major adverse CV events (MACE) or arrhythmias, neither in the clinical developmental program, nor in the retrospective observational cohort study (BA058-05-028), nor from the five and half years of post-marketing experience in the United States.

The transient increase in heart rate associated with abaloparatide, CV events of MI, stroke and arrhythmia are identified as potential safety risks in the European Union (EU)-Risk Management Plan (RMP) for abaloparatide. Therefore, to further evaluate these potential safety risks for abaloparatide, this post authorisation safety study (PASS) has been planned as an additional pharmacovigilance activity.

Research question and objectives

Research Question: Is the risk of major cardiovascular events (MACE-1 and MACE-2), arrhythmia, and all-cause mortality (including CV death) associated with abaloparatide use in women in routine clinical practice in Europe not different relative to teriparatide?

The primary objective of this study is to evaluate the risk of CV events of MACE-1 (defined as events of myocardial infarction (MI), stroke, or CV death), potentially associated with the use of abaloparatide, in comparison with the use of teriparatide in routine clinical practice. The study endpoints corresponding with this objective are:

- incidence rate (IR) of MACE-1 in:
    - new abaloparatide users in the population in Europe as per indication of the EU Summary of Product Characteristics (SmPC);
    - and separately in a cohort of new users of teriparatide who would also fulfil the indication/contraindications for abaloparatide as per the EU SmPC;
    - groups stratified by age;
    - groups stratified by pre-specified key CV risk factors (such as hypertension, hypercholesterolemia, diabetes, etc.).
- estimates of comparative risk, using an active comparator, new user design, of MACE-1, in new abaloparatide users in the indicated population in Europe as per the EU SmPC compared with new users of teriparatide (active comparator) with similar baseline characteristics.

The secondary objectives of this study are to evaluate the risk of MACE-2 (defined as events of MI, stroke, or all-cause mortality including CV death), MI, stroke, CV death, all-cause mortality

including CV death, and arrhythmia potentially associated with the use of abaloparatide in comparison with the use of teriparatide in routine clinical practice. The study endpoints corresponding with these objectives are:

- incidence rates (IR) of the following CV events: MACE-2, MI, stroke, CV death, all-cause mortality including CV death, and arrhythmia in:
    - new abaloparatide users in the indicated population as per the Summary of Product Characteristics (SmPC);
    - and separately in a cohort of new users of teriparatide who would also fulfil the indication/contraindications for abaloparatide.
    - groups stratified by age;
    - groups stratified by pre-specified key CV risk factors (such as hypertension, hypercholesterolemia, diabetes, etc.).
- estimates of comparative risk, using an active comparator, new user design, of CV events MACE-2, MI, stroke, CV death, all-cause mortality including CV death, and arrhythmia in new abaloparatide users in the indicated population in Europe as per the SmPC compared with new users of teriparatide (active comparator) with similar baseline characteristics.

Study design

We will perform an international network cohort study using data mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM). The study will use a "new users" design and compare new users of abaloparatide to new users of teriparatide.

The index date will be defined as the date on which the patient has a first prescription for either abaloparatide or teriparatide during the data identification period.

Study population

The study population comprises all women from the 4 participating databases with osteoporosis (OP) who are prescribed abaloparatide or teriparatide medication for the first time (new user) during the data identification period, have been continuously registered in the data source for at least 12 months prior to the index date, and are at least 50 years of age on the date of the first prescription of abaloparatide or teriparatide. Women with a pre-existing record of hypercalcaemia, severe renal impairment, diagnosis of Paget disease of the bone or any malignancy (except for non-melanoma skin cancers) at any time before treatment initiation will be excluded.

New users will be followed for a maximum of 19 months (18 months after index date plus 30 additional days) from index date. An exposure-based follow-up period will be used for the estimation of CV IRs.

For the purpose of data analyses, patients will be followed until first occurrence of the CV event of interest, discontinuation, switching or addition of any other OP medication (except calcium/vitamin D supplements), loss to follow-up, death, end of the 19 months of follow-up from index date, or end of the data identification period/data extraction date.

Variables

The medications of interest include abaloparatide (target therapy) and teriparatide (active comparator). Primary outcome is MACE-1 (first occurrence of MI, stroke, or death due to CV causes). Secondary outcomes are MI, stroke, death due to CV causes, all-cause mortality, MACE-2 (first occurrence of MI, stroke, or death (all-cause including CV death)), and arrhythmia.

Other key covariates and potential confounding factors will be identified at index date based on the patients' records prior to index date, and will include general patient characteristics, CV risk factors, markers of OP severity, use of other medications, and any other predictors of treatment with abaloparatide as described in detail in Section 9.3.3.

Data sources

This study will be conducted using routinely collected data from different data sources. Data from countries (Spain, Germany and UK) will provide heterogeneous and representative data on the safety of abaloparatide. Data from primary care records (Spain), primary care linked with hospital admission data (UK) and outpatient records (Germany) will be used. US data will be included in the 1st interim report, for contextualisation.

Study size

Feasibility estimates demonstrate the capability of the data sources to capture a sufficient number of users of abaloparatide or teriparatide. The number of abaloparatide users and teriparatide (comparator) users needed to obtain an alpha risk of 0.025 with 90% power in a 1:5 (abaloparatide: teriparatide) matched cohort analysis for different scenarios of incidence rate of CV events at the end of 18 months and non-inferiority margin based on the hazard ratio (HR) were calculated. In the worst-case scenario of IRs of 4 per 100 person-years and a non-inferiority margin of 3, 112 abaloparatide users and 555 users of teriparatide users would be required.

Data Analysis

The data identification period will cover from the second quarter (Q2) of 2024 until the latest data release available in each of the contributing databases. The IRs of CV events of interest for abaloparatide or teriparatide will be calculated. IR and 95% confidence intervals (CIs) of CV events of interest will be calculated for both study drug users using a Poisson model.

The CV event rates for each study drug will also be provided stratified by age groups and key CV risk factors. In addition, large-scale propensity scores (PS) will be estimated using Lasso logistic regression, and the resulting PS will be used to match comparable participants. Then, Cox regression models conditioned on the matched sets will be used to calculate hazard ratio and 95% confidence interval (CI) for each of the study outcomes according to exposure status.

Milestones

The number of abaloparatide and teriparatide users will be monitored and reported annually in a total of 3 reports (two interim reports and a final report). Upon the minimum sample size being reached, the comparative safety analysis will be conducted and reported as part of the next interim and/or final report/s. The study will continue to completion even if the sample size is reached before the 3 years to allow variability and better precision in the estimates of IR and HR.

Data from US will be included in the 1st interim report for contextualisation.

5 AMENDMENTS AND UPDATES

This protocol was updated primarily to address the comments provided in the CHMP Assessment Report dated 18 September 2025 for the PASS protocol for Eladynos.

Substantial changes in PASS Protocol version 6.0 compared with PASS protocol version 5.0 are summarized in the table below.

All other changes are editorial in nature and were made to ensure consistency and clarity within the protocol. These changes are shown in the redline version of PASS Protocol version 6.0 but are not summarised in the table.

Amendment number	**Date**	**Protocol Section**	**Summary of Change**	**Justification for Change**
1 (Protocol V2.0)	29 September 2023	Title page	Title of protocol has been changed from "**European non-interventional post-authorization safety study to assess cardiovascular events and all-cause mortality in patients exposed to abaloparatide or teriparatide** to "**European non-interventional post-authorization safety study to evaluate cardiovascular events in patients newly exposed to abaloparatide or teriparatide"**	The change more accurately reflects the new research question and the updated objectives.
		PASS Information Section 4 Abstract	A research question has been added and the primary and secondary objectives have been further clarified.	To address CHMP Assessment Report request for clear statements regarding the research question and objectives, to state that the primary objective involves

Amendment number	Date	Protocol Section	Summary of Change	Justification for Change
		Section 8 Research Question and Objectives		MACE-1, and to list the specific components of the CV events of interest.
		Section 4 Abstract Section 9.3.2 Study Outcomes	The new primary outcome is MACE-1. All other CV events of interest are secondary outcomes.	To align with the updated research question and objectives.
		Section 6 Milestones	The milestones and milestone dates have been updated and clarification regarding the contents of the interim reports has been added.	To address CHMP Assessment Re-port request for the format of the table to conform with the current guidance and to confirm that progress reports will be included in each interim report. The new milestone dates reflect the latest information regarding the planned launch date of abaloparatide in the EU.
		Section 7.1 Product Section 7.2 Regulatory action Section 7.3 Previous observational studies	Background information regarding the incidence of CV events in previous studies has been added.	To address CHMP Assessment Re-port request for justification for conducting the PASS.
		Section 9.2.6 Exclusion criteria	The exclusion criteria have been expanded from 3 to 6 criteria.	To align with the contraindications stated in the SmPC for Eladynos, while

Amendment number	Date	Protocol Section	Summary of Change	Justification for Change
				taking into account the variables that are available in the participating databases.
		Section 9.3.1 Exposure	Figure 1 (Diagram of exposure to abaloparatide or teriparatide) has been added.	To address CHMP Assessment Re-port request for a diagram of the exposure periods.
		Section 9.3.1 Exposure	Information regarding the administration route, biology, and half-life of abaloparatide and teriparatide has been added.	To address CHMP Assessment Report request to add information on the administration route, biology, and half-life of abaloparatide and teriparatide.
		Section 9.3.3.1 Potential confounders	The list of potential confounders has been removed from the protocol. The information is now in the SAP.	Details regarding the potential confounders are more appropriately discussed in the SAP.
		Section 9.5 Study size	The sample size considerations have been updated to reflect the new primary outcome of MACE-1.	To align with the primary objective, which involves MACE-1.
		Section 9.7.1.3.1 Negative control outcomes	The list of potential negative control outcomes has been removed from the protocol. The information is now in the SAP.	Details regarding the potential negative control outcomes are more appropriately discussed in the SAP.

Amendment number	Date	Protocol Section	Summary of Change	Justification for Change
		Section 9.7.1.4 Sensitivity analysis	A new section regarding sensitivity analysis has been added.	To provide information regarding the sensitivity analyses that are planned.
		Appendix 3 Preliminary Code List of Study	Appendix 3 has been removed from the protocol. The code lists are now in the SAP.	The final code lists are more appropriately discussed in the SAP.
2 (Protocol version 3.0)	20 February 2024	Section 4 Abstract Section 8 Research question and objectives	Integrated the endpoints into the objectives.	The change more accurately reflects how the objectives will be achieved through the endpoints.
		Title Page Section 4 Abstract Section 8 Research question and objectives	Replaced word 'characterise' with 'evaluate'	To address CHMP Assessment Report request to make the section more specific.
		Section 9.3.3.1 Potential confounders	Added list of specific confounders (covariates) to be included in the propensity score matching models.	To address CHMP Assessment Report request to add specific list of covariates.
		Section 3 Responsible Parties	Added Nicola Barclay as Study coordinator to listed parties	Nicola Barclay is included in the study team from Oxford from January 2024.

Amendment number	Date	Protocol Section	Summary of Change	Justification for Change
		Section 9.5 Study Size	More detail added to study size with predicted teriparatide users in 2026	To address CHMP Assessment Report related to the SAP regarding predicted users.
3 (Protocol version 4.0)	20 June 2025	Title Section 3 Participating countries Section 4 Abstract Section 6 Table 1 Section 9.2 Setting Section 9.4 Data sources Section 10 Protection of Human Subjects	Title changed to "**European and US non-interventional post-authorization safety study to evaluate cardiovascular events in patients newly exposed to abaloparatide or teriparatide"** Removal of database from Italy and France; inclusion of CPRD Aurum (UK) and PharMetrics® Plus (US). Addition of UK and US throughout document where databases and population are mentioned.	Data partner (IQVIA) no longer has access to database (LPD Italy) Abaloparatide will not be launched in France. Feasibility counts indicate sufficient numbers in CPRD Aurum and PharMetrics® Plus.
		Milestones	Interim report 1 and 2 submission date delayed by 6 months. Data availability updated to more recent data 6 months prior to report submission	Addition of new data partners require contracting and ethics approval before data can be extracted.
		Title	Title changed to "**European and US**	Addition of US database from previously

Amendment number	Date	Protocol Section	Summary of Change	Justification for Change
4 (Protocol version 5.0)	16 October 2025		**non-interventional post-authorization safety study and all-cause mortality to evaluate cardiovascular events in patients newly exposed to abaloparatide or teriparatide"**	approved protocol version 3.0. Addition of all-cause mortality in response to CHMP Assessment Report to be in line with the title in the RMP.
		Section 6 Milestones	Updated data periodicity and availability of CPRD Aurum in Table 1	Details provided by CPRD
		Section 9.9.2 Information bias	Further elaboration on limitation on lack of death data in PharMetrics® Plus (US) and DA Germany and effect on study results.	In response to CHMP Assessment Report
5 (Protocol version 6.0)	23 February 2026	Section 4 Abstract Section 6 Table 1 Section 9.2 Setting Section 9.4 Data sources	US PharMetrics® Plus to be used only for contextualisation in the 1st interim report	In response to CHMP Assessment Report
		Section 4 Abstract Section 5 Study size	Sample size updated to provide sample sizes according to	In alignment with text in Section 5 "to demonstrate noninferiority using a margin of 3"

Amendment number	Date	Protocol Section	Summary of Change	Justification for Change
			non-inferiority design rather than the superiority design	
		Section 3 Responsible Parties	Added Mahkameh Mafi as Study manger to listed parties	Mahkameh Mafi is included in the study team from Oxford from June 2025.
6 (Protocol version 7.0)	14 July 2026	Section 6 Study period	Extended the study duration from 3 years to 6 years	To address CHMP Assessment Report related to the study duration.

6 MILESTONES

Milestone	Planned date*
Start of data collection	Q2 2024
End of data collection	Q3 2030
Interim report 1 – explanatory features of dataset (year 1)	Data available up to end Q4 2025/ submission end Q2 2026
Interim report 2 – explanatory features of dataset (year 3)	Data available up to end Q4 2027/ submission end Q2 2028
Interim report 3 – explanatory features of dataset (year 4)	Data available up to end Q4 2028/ submission end Q2 2029
Final report of study results	Data available up to end Q3 2030/ submission Q1 2031

EMA=European Medicines Agency; EU=European Union; PAS=post-authorization study.
*The final dates for the milestones will be included after the protocol is approved by EMA.

In addition to preliminary/interim findings, the proposed interim reports will include information on the progress of the study, and any changes/amendments.

Milestones have been planned to maximise the efficiency and availability of data retrieval from the different data sources. A summary of such information is provided here:

Table 1: Overview of the timing of data updates from participating data sources

Data source (Country)	Periodicity of updates	Time of the year when updates are released	Data availability for each update
SIDIAP (Spain)	Every 6 months	June and December	End of previous calendar year (in June); up to June in December
IQVIA DA (Germany)*	Quarterly	Jan / Apr / Jul / Oct	Until month M-4
CPRD Aurum CDM Version (UK)	Every 6 months	June and December	Until month M-3
IQVIA PharMetrics® Plus (US)*, **	Quarterly	Mar / Jun / Sep / Dec	Until month M-6

CPRD=Clinical Practice Research Datalink; DA=Disease Analyser; M=month; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària

* Periodicity, timing and data availability of updates may change depending on refresh schedules planned on an annual basis

** to be used only for contextualisation in the 1st interim report

7 RATIONALE AND BACKGROUND

7.1 Product

Abaloparatide is a peptide that selectively binds to the receptor conformation, called RG, of the parathyroid hormone type 1 receptor (1, 2). Abaloparatide was registered and approved in the United States and Japan since 2017 and 2022, respectively. Abaloparatide also received approval in the EU on 12th of December 2022 for the treatment of osteoporosis in postmenopausal women at increased risk of fracture.

In postmenopausal women (age ranged from 49 to 86) with osteoporosis (OP) and previous fractures, abaloparatide was superior to placebo in reducing new vertebral and non-vertebral fracture risk (Study BA058-05-003 [ACTIVE]) (3). After 18 months, 0.51% of those treated with abaloparatide had a new vertebral fracture compared with 4.17% in the group who received placebo.

Abaloparatide is indicated for the treatment of OP in postmenopausal women at increased risk of fracture and with the following contraindications per SmPC: hypersensitivity to the active substance(s) or to any of the ingredients, hypercalcaemia, severely reduced kidney function or unexplained high levels of alkaline phosphatase, in addition to patients at risk for osteosarcoma, with skeletal malignancies or bone metastases.

Abaloparatide was associated with transient increases in heart rate in the pivotal study (Study BA058-05-003) (3). The mean increase in heart rate from baseline in the abaloparatide group ranged, from Day 1 to Month 12, between 6.9 and 7.8 bpm at one-hour post-injection compared to 1.0 and 1.9 bpm in the placebo group. In the thorough QT study (Study BA058-05-012), the

increase in heart rate with abaloparatide was observed within 4 hours following injection. However, previous studies did not provide supporting evidence for a causal relationship between these transient increases in heart rate and an increased risk of MACE, or arrhythmias (4-6). These included one phase 3, pivotal clinical trial of abaloparatide in postmenopausal women with osteoporosis (Study BA058-05-003) and its extension (Study BA058-05-005), one phase 3 clinical trial in postmenopausal women and men with osteoporosis in Japan (Study ITM-058-301) and one retrospective observational cohort study using US claims data (Study BA058-05-028 and its extension (7)).

In addition, from the latest aggregate report (DSUR #12) submitted on the 25th of February 2023, the cited post-marketing experience through November 2022 showed over 57,900 patient-years of exposure to abaloparatide. The evaluation of cumulative safety information from this report concluded that the benefit-risk profile of abaloparatide remains favourable and consistent with the previous cumulative experience.

The transient increase in heart rate associated with abaloparatide, CV events of MI, stroke and arrhythmia are identified as potential safety risks in the EU- RMP for abaloparatide. To evaluate the risk for CV safety events of MI and stroke, and all-cause mortality [including CV death] associated with the use of abaloparatide in clinical practice compared with teriparatide, a multinational, multi-database, comparative PASS will be conducted.

7.2 Regulatory action

This CV PASS is part of a PASS program aimed at monitoring the safe use of abaloparatide in the international population within the framework of a comprehensive RMP.

While there was no evidence for an increase in the incidence of serious CV events in the pivotal study in women, subjects with clinically significant EKG abnormalities or those with cardiovascular disease to a degree that would compromise safety, in the opinion of the investigator, were excluded. Consequently, the number of CV events in the study population may have been too low to fully assess the risk of serious CV events related to the transient increase in heart rate following dosing. This PASS will further quantify the potential risk of serious CV events and arrhythmias with abaloparatide in comparison to teriparatide in clinical practice.

7.3 Previous observational studies

This will be the first PASS to describe the risk of CV events (MI and stroke), all-cause mortality including CV death and arrhythmia among abaloparatide users in clinical practice in Europe. A previous observational study was conducted in the United States, which showed no evidence of differential CV risk amongst abaloparatide compared to teriparatide users (6). Routine post marketing pharmacovigilance (PV) data are being collected in parallel in US, where abaloparatide was approved for the treatment of postmenopausal women with osteoporosis at high risk for fracture in 2017 and then in 2022, in men with osteoporosis at a high risk for fracture or patients who have failed or are intolerant to other available osteoporosis therapy.

Both the observational study and post-marketing data have limitations, including lack of mortality data outside of hospitals and no access to income and education data.

8 RESEARCH QUESTION AND OBJECTIVES

Research Question: Is the risk of major cardiovascular events (MACE-1 and MACE-2), arrhythmia, and all-cause mortality (including CV death) associated with abaloparatide use in routine clinical practice not different relative to teriparatide?

The primary objective of this study is to evaluate the risk of CV events of MACE-1 (defined as events of myocardial infarction (MI), stroke, or CV death), potentially associated with the use of abaloparatide, in comparison with the use of teriparatide in routine clinical practice. The study endpoints corresponding with this objective are:

- incidence rate (IR) of MACE-1 in:
    - new abaloparatide users in the indicated population as per the Summary of Product Characteristics (SmPC);
    - and separately in a cohort of new users of teriparatide who would also fulfil the indication/contraindications for abaloparatide .
    - groups stratified by age;
    - groups stratified by pre-specified key CV risk factors (such as hypertension, hypercholesterolemia, diabetes, etc.).
- estimates of comparative risk, using an active comparator, new user design, of MACE-1, in new abaloparatide users in the indicated population as per the SmPC compared with new users of teriparatide (active comparator) with similar baseline characteristics.

The secondary objectives of this study are to evaluate the risk of MACE-2 (defined as events of MI, stroke, or all-cause mortality including CV death), MI, stroke, CV death, all-cause mortality including CV death, and arrhythmia potentially associated with the use of abaloparatide in comparison with the use of teriparatide in routine clinical practice. The study endpoints corresponding with this objective are:

- incidence rates (IR) of the following CV events: MACE-2, MI, stroke, CV death, all-cause mortality including CV death, and arrhythmia in:
    - new abaloparatide users in the indicated population as per the Summary of Product Characteristics (SmPC);
    - and separately in a cohort of new users of teriparatide who would also fulfil the indication/contraindications for abaloparatide.
    - groups stratified by age.
    - groups stratified by pre-specified key CV risk factors (such as hypertension, hypercholesterolemia, diabetes, etc.).

- estimates of comparative risk, using an active comparator, new user design, of CV events MACE-2, MI, stroke, CV death, all-cause mortality including CV death, and arrhythmia in new abaloparatide users in the indicated population as per the SmPC compared with new users of teriparatide (active comparator) with similar baseline characteristics.

9 RESEARCH METHODS

9.1 Study Design

This will be a multinational, network (federated), active-comparator new user cohort study comparing abaloparatide to teriparatide.

This study design is conforming with the guidelines on methodological standards set by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) for research in pharmacoepidemiology (EMA/95098/2010, Rev. 10) (8).

- As outlined in Section 8, estimates of the IR of CV events MACE-1, MACE-2, MI, stroke, CV death, all-cause mortality including CV death, and arrhythmia in new abaloparatide users adherent to the indicated population in the SmPC and in new users of teriparatide who would also be eligible for abaloparatide as per the approved SmPC will be calculated to address the study objectives.

- In addition, the two treatment cohorts (abaloparatide and teriparatide) will be matched on propensity scores, to compare the risk of all study outcomes in new users of abaloparatide adherent to the indicated population per the SmPC to comparable new users of teriparatide who would also be eligible for abaloparatide per the approved SmPC and with similar baseline characteristics. This approach has been proposed and is widely accepted to minimize confounding including confounding by indication in observational drug safety research (9) and aligned with ENCePP methodological guidelines for pharmacoepidemiology (EMA/95098/2010, Rev. 10) (8). The baseline variables considered as potential confounders in the PS matching are discussed in Section 9.3.3.1 and include previous use of OP medications. The full list of OP medications of interest is provided in the Statistical Analysis Plan (SAP).

Details regarding the planned study analyses are provided in the SAP.

9.2 Setting

Participants from 3 European countries will be included. Data from the following 4 electronic healthcare/claims databases from 4 countries will be obtained for this study: the Information System for Research on Primary Care (SIDIAP) from Spain, IQVIA Disease Analyzer (DA) from Germany, the Clinical Practice Research Datalink (CPRD) Aurum linked with Hospital Episode Statistics (HES) from the UK, and IQVIA PharMetrics® Plus (PMTX+) from the United States (US) – for contextualisation only (see Section 9.4 Data Sources below for more details).

All data sources are mapped to the OMOP CDM. The benefits of this standardisation are that contributing centres can participate in distributed network analyses without sharing patient-level information, and that data provenance can be ensured while applying common analytical code across all data sources in a consistent manner (10-12)

9.2.1 Source population

All women registered in 1 of the 4 contributing data sources for at least 12 months prior to index date and included in the same data source during the identification period, will be eligible as source population.

9.2.2 Study period

Although the marketing authorization of abaloparatide was granted in Europe on 12th December 2022, the launch date in the first of the participating countries started in the second quarter of 2024 (Q2 2024). Therefore, the data identification period (start of study period) will cover from Q2 2024, and it will end with the most recent version of data that is available within each of the databases at the end of the study. Further information on the relevant dates of the study by country is presented in the SAP.

Three annual interim/progress reports and the final report will be submitted. Preliminary results and any changes/amendments will be reported in the form of annual interim/progress reports within the first 5 years. Upon the minimum sample size being reached as set out in Section 9.5, the comparative safety analysis will be conducted and reported as part of the next interim/progress and/or final report/s. The study may be prolonged to up to 5 years, if insufficient number of patients or/and events are seen at the end of the study.

9.2.3 Study population

The study population represents the indicated population for abaloparatide as per the EU SmPC and therefore comprises postmenopausal women from the source population who are first prescribed abaloparatide or teriparatide medication (new user) during the identification period.

Patients must have been continuously registered in the data source for at least 12 months prior to the first recorded prescription of the OP medication of interest and are at least 50 years of age on the date of the prescription.

Osteoporosis medications of interest are abaloparatide and teriparatide and will be identified through specific codes in prescription records. Patients in each cohort (new users of abaloparatide or teriparatide) will be followed from the date of the first prescription of the index study drug during the data identification period.

For the purposes of this study, a patient will be considered a new user if she did not receive abaloparatide or teriparatide in the 12 months prior to her first prescription of abaloparatide/teriparatide during the identification period.

9.2.4 Index date

The index date will be defined as the date on which each identified new user receives the first prescription for abaloparatide or teriparatide during the data identification period.

9.2.5 Inclusion criteria

New users of abaloparatide and teriparatide during the identification period will be identified. All the following inclusion criteria must be met for participants to enter the study:

- Women aged 50 years or older at the index date.
- At least 12 months of eligibility in the database before index date with continuous enrollment.

9.2.6 Exclusion criteria

Exclusion criteria are as follows (ascertained at any time prior to index date, unless otherwise indicated):

- Pre-existing hypercalcaemia.
- Severe renal impairment (Stage 3b CKD or worse or dialysis)
- Patients with skeletal malignancies or bone metastases.
- Patients who have received radiation therapy.
- Patients with a diagnosis of Paget's disease of the bone or unexplained elevations of serum alkaline phosphatase.
- Patients who received abaloparatide or teriparatide during the 12 months prior to their first prescription of abaloparatide/teriparatide (index date).

9.2.7 Follow-up

New users of abaloparatide or teriparatide will be followed for a maximum of 18 months (while on treatment) plus 30-day follow-up (while off treatment; for a total of 19 months) from index date. Switching to other new OP medication (except calcium/vitamin D supplements) will result in censoring of the data for the patient. The full list of other OP medications of interest is provided in the SAP.

The main analysis in this study will be performed as treated, where patients will be followed until first occurrence of the CV event of interest, discontinuation of the study drug of interest, switching or addition of any other OP medication (except calcium/vitamin D supplements), lost to follow-up, death, end of the 18 months of follow-up (as per the abaloparatide SmPC) plus 30-day follow-up, or end of the data identification period/data extraction date. At the point of switching treatment a patient is censored for that arm of the study in this analysis.

9.3 Variables

Variables in each data source will be assessed according to the OMOP CDM schema (see Section 9.6 for more detail), which contains a set of tables named "Standardised Vocabularies" which are designed to store the standard vocabularies as well as additional information.

9.3.1 Exposure

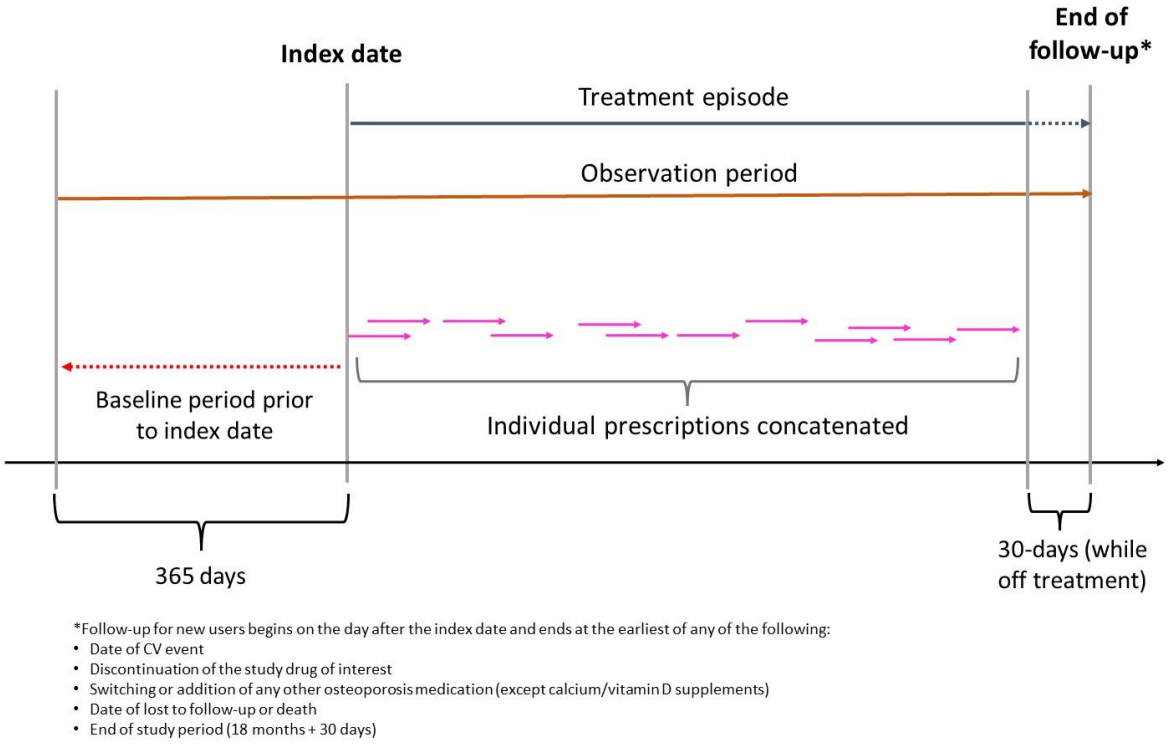
Abaloparatide and teriparatide are the OP medications of interest in this study.

The ATC code lists for the identification of the exposure variables (abaloparatide and teriparatide) are detailed in the SAP.

While a number of the databases contain information on drug dispensing, for ease of description we refer to data as relating to "prescriptions" throughout the protocol.

Exposure to the study drug will commence on the index date, i.e., date of the first prescription for the study drug without any record of the same study drug use during the baseline period (previous 12 months to the index date). The end of exposure will be defined as the date of the last prescription for the study drug plus the number of doses prescribed in that last prescription (Figure 1). Therefore, the duration of exposure (days) will be the date of last study drug prescription plus the calculated number of exposure days provided in the last prescription minus the index date.

Figure 1: Diagram of exposure to abaloparatide or teriparatide



*Follow-up for new users begins on the day after the index date and ends at the earliest of any of the following:
- Date of CV event
- Discontinuation of the study drug of interest
- Switching or addition of any other osteoporosis medication (except calcium/vitamin D supplements)
- Date of lost to follow-up or death
- End of study period (18 months + 30 days)

Abaloparatide is a 34 amino acid peptide that shares 41% homology to parathyroid hormone [PTH(1-34)] and 76% homology to parathyroid hormone related peptide [PTHrP(1-34)], and is an activator of the PTH1 receptor signaling pathway. Abaloparatide stimulates new bone formation on trabecular and cortical bone surfaces by stimulation of osteoblastic activity. The median (range) time to peak concentration of abaloparatide 80 micrograms is 0.5h (0.25 to 0.52 h) following subcutaneous administration. The volume of distribution is approximately 45 L. The mean half-life of abaloparatide is about 1 h. The peptide fragments are primarily eliminated through renal excretion.

The recommended dose of abaloparatide is a daily subcutaneous (SC) injection by the patient for 18 months. Each dose (40 microliters) contains 80 micrograms/dose solution of abaloparatide for injection and it is delivered via a pre-filled pen. Each pre-filled pen contains 3 mg of abaloparatide in 1.5 mL of solution (corresponding to 2 milligrams per mL). The pen should not be used for more than 30 consecutive days. In addition, it requires no refrigeration after first use and should not be used for longer than 30 days after first use.

Teriparatide (rhPTH(1-34) is the active fragment of endogenous human PTH. The recommended dose is 20 micrograms administered once daily for a maximum total duration of treatment of 24 months. The volume of distribution of teriparatide is approximately 1.7 L/kg and the half-life is approximately 1 hour when administered subcutaneously, which reflects the time required for absorption from the injection site. Teriparatide is eliminated through hepatic and extra-hepatic

clearance (approximately 62 L/h in women and 94 L/h in men). Branded and generic teriparatide will be included in the teriparatide cohort for this study.

For all objectives, follow-up will start with the first prescription of either abaloparatide or teriparatide, regardless of previous other OP drug use. A switch from abaloparatide or teriparatide to any other OP drug will result in censoring of the data for analyses.

Drug discontinuation will be defined as no prescription at least for one month after the end of exposure, with end of exposure estimated as the date of the last prescription plus the number of doses prescribed in that last prescription. Drug discontinuation will also be considered at the date when a concomitant second OP medication is added.

9.3.2 Study outcomes

Primary outcome: incidence of MACE-1 (defined as events of MI, stroke, or CV death)

The *secondary outcomes* are the incidence of:

- MI
- Stroke
- Death associated due to CV causes.
- All-cause mortality.
- MACE-2 (defined as events of MI, stroke, or death (all cause including CV death)).
- Cardiac arrhythmias

The IR and 95% CI of the above study outcomes will be calculated for abaloparatide and for teriparatide using a Poisson model.

From the above listed CV events, MACE-1 will be considered in the comparative analysis as the primary outcome while MI, stroke, CV death, all-cause mortality, MACE-2, and arrhythmia will be considered as secondary outcomes.

Study outcomes were developed and used in an ongoing PASS study with similar study population and endpoints led by University of Oxford (13). The code lists for the identification of MI, stroke and arrhythmia are fully detailed in the SAP.

As for CV death, SIDIAP and CPRD Aurum will combine diagnosis codes (for hospital admission/primary care records) respectively with mortality using a time specific window to define cardiovascular death.

For CPRD Aurum and SIDIAP, if the date of CV events occurs within a window of 60 days prior to the date of mortality, cause of death will be assumed to be related to these respective conditions (i.e., mortality related to CV events). Further details regarding the determination of CV death are provided in the SAP.

9.3.3 Covariates (confounders)

9.3.3.1 Potential confounders

The complete list of key features to be added in the propensity score equation, which will include predictors of fracture as well as CV risk factors is included below and in more detail in the SAP. This list of potential key confounders has been identified a priori based on recent work on the identification of key CV risk factors amongst women with OP (14, 15), led by University of Oxford. Details regarding the identification of CV risk factors that are potential confounders in the various data sources are provided in the SAP. We will also conduct a data-driven approach to explore if additional demographics, diagnoses, and medications are predictive of the study medication assignment through large-scale regularised regression (15). Details regarding PS matching described in Section 9.7.1.2.1.

List of potential covariates:

General characteristics (as measured at index date or in the previous year):

- Socio-demographics: age, ecological deprivation index (where available).
- Number of previous general practitioner (GP) visits.
- Number of previous hospital visits (where available).

CV risk factors:

- BMI/obesity (most recent measure or diagnosis of obesity as recorded in the previous 5 years)
    - Smoking (most recent measure or diagnosis of smoking as recorded in the previous 5 years).
    - Alcohol dependency (most recent diagnosis of alcoholism/alcohol drinking problems as recorded in the previous 5 years)
- Hypertension: diagnosis recorded prior to index date or 2 or more recorded measures of systolic blood pressure >140mmHg; or 2 or more measures of diastolic blood pressure >90mmHg (16) in the year before index date.
- Use of antihypertensives prescribed in the year prior to index date: alpha blockers, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers.
- Type 2 diabetes mellitus: diagnosis recorded prior to index date or 2 or more recorded measures of HbA1c ≥6.5%.
- Type 1 diabetes mellitus: diagnosis recorded prior to index date.
- Use of antidiabetic medications (excluding insulin) prescribed in the year prior to index date.

- Hypercholesterolaemia/dyslipidaemia: a diagnosis recorded prior to index date or the presence of 1 or more measurements of raised level of total cholesterol, LDL cholesterol or triglycerides in the year before index date.
- Use of lipid-lowering drugs as prescribed in the year before the index date.
- History of atrial fibrillation will be defined based on any records of atrial fibrillation before index date.
- History of cardiac arrhythmia other than atrial fibrillation will be defined based on any previous records before index date.
- History of MI or stroke before index date.
- Established CVD any time prior to index date. It will include angina and atherosclerosis.

Markers of disease severity (risk factors for OP/fractures):

- Number of previous fracture/s (hip, vertebral, major osteoporotic, other/s) at any time prior to index date.
- Number of major osteoporotic fractures at any time prior to index date (17, 18).
- Severe OP or high risk of fracture, defined as presence of 1 or more major osteoporotic fractures in the year prior to index date.
- Previous use of medications for OP in the year prior to index date.
- Use of systemic glucocorticoids prescribed in the year prior to index date.

Other medication that has an effect on bone

- Previous use of prescribed vitamin D supplements in the year prior to index date.
- Previous use of prescribed calcium supplements in the year prior to index date.
- Previous use of prescribed calcium and vitamin D (combination) supplements in the year prior to index date.
- Use of systemic sex hormone therapy prescribed in the year prior to index date.

All covariates will be identified at index date based on previous patients' records and potentially included as covariates in the proposed propensity score models. Co-morbidities will be identified on the basis of prespecified Systemized Nomenclature of Medicine (SNOMED) codes and previous medication use will be characterised using RxNorm codes.

Large scale propensity scores will be estimated for each data source separately to maximize the richness and granularity of each data source, and to capture as much information as possible on the key features prespecified below as well as any database-specific predictors of treatment. This approach has been previously validated in methodological research (19).

9.3.3.2 Stratification terms

The CV event/s rates of MACE-1, MACE-2, MI, stroke, CV death, all-cause mortality including CV mortality, and arrhythmia will also be provided stratified by 5-year age bands and key CV risk factors.

The IRs and 95% CI of CV events of interest of MACE-1, MACE-2, MI, stroke, CV death, all-cause mortality including CV mortality, and arrhythmia will be calculated as described in Section 9.2.7. Stratification will be conducted based on the following baseline characteristics:

- Age (on the index date), stratified by database-specific 5-year age bands.
- Prior use of OP medication: prior OP medication use was defined as at least 1 prescription for an OP medication other than abaloparatide or teriparatide within 1 year prior to index date.
- Previous history of MI.
- Previous history of stroke
- Previous history of "other" CV events (arrhythmia, ischemic heart disease, heart failure, cerebrovascular disease, peripheral vascular disease, established cardiovascular disease, and thromboembolism; all CV events except sudden CV death, MI, and stroke).
- Previous history of arrhythmia.
- Previous history of type 2 diabetes mellitus.
- Previous history of hypertension.
- Previous history of hypercholesterolaemia.

Further stratification variables will be defined to capture all relevant CV risk factors if requested and in agreement with the regulatory authorities.

9.4 Data sources

This study will be conducted using routinely collected data from different data sources that are mapped to the OMOP CDM. This enables federated analytics without transferring any patient-level data. These same principles and common data model are used in the DARWIN EU initiative, and in previous EMA-funded tenders.

The proposed databases have been selected based on their geographic location, the availability of longitudinal population-based data on drug utilization, number of teriparatide users available (to ensure sufficient statistical power for this study), their ability to capture abaloparatide use, the study outcomes, and the potential size of the study population, as well as their experience in previous multi-database studies on both drug utilization and safety.

These databases will provide representative clinical information as collected in routine clinical practice in four different healthcare settings in Europe. A tabulated overview of the information that will be derived from each database is provided in the SAP.

Three countries from different European areas are included, to provide heterogeneous and representative data on the safety of abaloparatide. An additional database from the US will be included in the 1st interim report for contextualisation. Similar to the pivotal clinical trial (ACTIVE)(3) which included patients from multiple countries including the US and European countries, we do not expect the causal effects to be different across populations. From previous studies in the US (7) and Europe (20), the populations using osteoporosis treatment have similar age range, and prevalence of comorbidities such as hypertension, osteoporosis, and fractures. Any difference in patient characteristics will be accounted for with propensity score matching between the treatment groups within each database and meta-analysis of the results if the heterogeneity is low.

All of the chosen databases comply with EU guidelines on the use of medical data for medical research and have been validated for pharmacoepidemiological research (21-23).

The confirmed participating databases will be SIDIAP (Spain), IQVIA DA (Germany), CPRD Aurum (UK), and IQVIA PharMetrics® Plus (US) (for contextualization only). Table 2 provides an overview of key elements of these databases. The total number of persons actively registered in the source population of these 4 databases together was 55 million.

Table 2: Overview of the study databases

Country	Spain	Germany	UK	US
Data source	SIDIAP	IQVIA DA	CPRD Aurum	IQVIA PMTX+
Type of database	MR	MR	MR	Claims
Active patients (millions)	5.8	8.3	16.7	24.4
Age categories	≥15 years	All	All	All
Date in	Yes	Yes	Yes	Yes
Date out	Yes	Yes	Yes	Yes
Date of death	Yes	No	Yes	No
Outpatient treatment/s	Yes (dates of prescription and dispensing)	Yes (date of prescription)	Yes (date of prescription)	Yes (date of prescription)
Hospitalisation	Yes	Incomplete coverage	Yes	Yes
Outpatient diagnoses	Yes	Yes	Yes	Yes
Coding of disease	ICD-10 (ICD-9 for hospital diagnoses)	ICD-10	SNOMED	ICD-9-CM/ICD-10-CM
Cause of death	No	No	No	No

ADM=administrative; ATC=Anatomical Therapeutic Chemical; DA=Disease Analyzer; ICD=International Classification of Diseases; ICD-10=ICD, revision 10; ICD-9=ICD, revision 9; MR=medical records; PMTX+ =PharMetrics® Plus; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària

9.4.1 SIDIAP, Spain

The GPs play an essential role in the public health care system of Spain as they are responsible for primary health care, long-term prescriptions and specialist and hospital referrals. The Spanish public health care system covers more than 98% of the population. The SIDIAP database comprises of electronic medical records (EMRs) of a representative sample of patients attended by GPs in Catalonia (North-East Spain), covering a population of more than 5.8 million patients (over 80% of the total of 7.5 million population of Catalonia) from 274 primary care practices with 3,414 participating GPs. The SIDIAP data comprises the clinical and referral events registered by primary care health professionals (GPs and nurses) and administrative staff in EMRs, comprehensive demographic information, prescription and corresponding pharmacy invoicing data, specialist referrals, primary care laboratory test results, and hospital admissions and their major outcomes.

Health professionals gather this information using ICD-10 codes and structured forms designed for the collection of variables relevant for primary care clinical management, such as country of origin, sex, age, height, weight, BMI, tobacco and alcohol use, blood pressure measurements, and blood and urine test results. Only GPs who meet quality control standards can participate in the SIDIAP database. Encoding personal and clinic identifiers ensures the confidentiality of the information in the SIDIAP database.

SIDIAP will be linked to the minimum basic set of hospital discharge data (CMBD- HA), which includes diagnosis and procedures registered during hospital admissions. Previous reports have shown the SIDIAP data to be useful for epidemiological research (22).

Studies performed using SIDIAP data require previous approval by both the Scientific and the Ethics Committee.

Further details regarding the SIDIAP database are provided in the SAP.

9.4.2 IQVIA DA, Germany

IQVIA™ Disease Analyser (DA) will be the German data partner for this study. The IQVIA DA database is collected from extracts of patient management software used by GPs and specialists practicing in ambulatory care settings. It contains daily-based anonymised records of relevant data, such as drug prescriptions, diagnoses, and basic medical and demographic data (24). The database covers approximately 3% of all practices in Germany and is representative of these practices with relatively similar characteristics (e.g., distribution of the age and sex of patients and prevalence of chronic physical conditions) (24).

Data coverage includes more than 45 million distinct person records out of a total population of 83 million (54.2%) in the country.

Patients visiting more than one provider are not cross identified for data protection reasons and therefore recorded as separate in the system. Dates of service include from 1992 through present. Observation time is defined by the first and last consultation dates.

Further details regarding the IQVIA DA database are provided in the SAP.

9.4.3 CPRD Aurum, UK

The UK patients' data will be sourced from CPRD Aurum and linked to HES where eligible. CPRD comprises computerised records of all clinical and referral events in both primary and secondary care in addition to comprehensive demographic information, medication prescription data (coded using dm+d codes), clinical events (coded using SNOMED codes), specialist referrals, hospital admissions and their major outcomes in a sample of UK patients. The prescription records include information on the type of product, date of prescription, strength, dosage, quantity, and route of administration.

Data from contributing practices are collected and processed into research databases. Quality checks on patient and practice level are applied during the initial processing. Patients with records showing ill-defined or non-continuous follow up, and missing or inconsistent registration information are excluded during this process. CPRD has a patient-level metric which assesses the recording and internal consistency of key variables including date of birth, practice registration date and transfer out date, and deems whether this is of acceptable quality for research (25).

Data are available for over 50 million patients including over 16.7 million currently registered patients which is considered to be representative of the UK population (26).

9.4.4 IQVIA PharMetrics® Plus, US

IQVIA PharMetrics® Plus (PMTX+) will be the US data partner for this study. The IQVIA PMTX+ database is a patient-centric, closed claims database of fully adjudicated pharmacy, hospital, and medical claims anonymized at the patient-level in accordance with the Health Insurance Portability and Accountability Act (HIPAA) sourced from commercial and other payers. As a longitudinal health plan database, it offers comprehensive views into diagnoses, treatments, and patient demographics, and is representative of the commercially insured US national population for patients under 65 years of age. Data coverage includes more than 110 million cumulative commercially insured population across all healthcare settings including inpatient, outpatient, emergency room, and pharmacy visits. Dates of service include from 2016 through present. Observation time is defined by the first and last consultation dates.

Data from this database will be used only for the 1st interim report, for contextualization.

9.5 Study size

Since this study will be undertaken using routinely collected data, all patients meeting the study inclusion/exclusion criteria previously described will be included. Table 3 illustrates the feasibility counts including the number of users of teriparatide available in each of the contributing databases selected for this PASS study. These can be used to inform the availability of the propensity-matched active comparator (teriparatide) in forthcoming data extractions. To predict how many teriparatide users may be present in each of the databases in future extractions we have drawn on data from an ongoing PASS study carried out by the University of Oxford which demonstrates that from 2018 to 2022 the incidence rates of teriparatide use has remained stable overtime. Based on these data, we have predicted the number of teriparatide users in 2026 to ac-

cumulate at least at a steady rate, and have included predicted numbers of cases in 2026 in Table 3. A current report indicates that the global teriparatide acetate market is expected to increase in the coming few years (27) therefore, our predicted number of cases is likely to be conservative. Using these predictions in European data sources, we will be able to, detect a non-inferiority margin of 3 based on the hazard ratio, across all levels of assumed incidence (outlined in Table 4).

Table 3: Current and predicted number of users of teriparatide in contributing databases.

	Teriparatide users	Data asset	Predicted teriparatide users in 2026
SIDIAP (ES)	1,412	2022	4,236
IQVIA DA (DE)	1,561	2022	4,683
CPRD Aurum (UK)	135	2022	405
IQVIA PharMetrics® Plus (US)*	16,451	2024	49,353

Note: Counts include all women and men who were using teriparatide in the respective year of the data asset. CPRD = Clinical Practice Research Datalink; DA=Disease Analyzer; DE=Germany; ES=Spain; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; UK= United Kingdom; US= United States
* to be used only for contextualisation in the 1st interim report

Abaloparatide has recently been launched in the participating countries. The sample size was calculated by considering different levels of assumed IRs of CV events, instead of using power. Table 4 shows the number of abaloparatide users and teriparatide users (comparator) needed to obtain an alpha risk of 0.025 with 90% power in a 1:5 (abaloparatide:teriparatide) matched cohort analysis for different scenarios of IR of CV events at the end of 18 months and effect size (HR). The range of incidence of CV events has been obtained from an ongoing PASS study where IRs of MACE-1 in new teriparatide users amongst women with severe OP ranged from 1 to 4 per 100 person-years.

The range of HR has been defined based on results from CV safety data from studies BA058-05-003 (ACTIVE) and BA058-05-028 (5, 6). These results show that there is no evidence of increased risk of MACE in patients treated with abaloparatide versus teriparatide (HR [95% CI]: 0.85 [0.23 to 3.15] and 1.00 [0.84 to 1.20] in studies BA058-05-003 and BA058-05-028, respectively). The study will be powered to provide additional confidence that, in those patients who received abaloparatide on label, there is no greater risk than that already characterised by this result and to demonstrate noninferiority using a margin of 3 (based on the upper limit 95%CI from the CV safety results obtained in the ACTIVE study (4)).

The number of participants needed will increase with decreasing IR of the safety event and with decreasing HR. Although all patients eligible in the proposed data sources will be included, the consequence of this is that lower risk scenarios will result in a delayed conclusion of the study. Conversely, high risk scenarios defined by high incidence of CV events and high attributable

risk, would result in a swift analysis: indeed, the worst-case scenario of IRs of 4 per 100 person-years and a 3-fold relative increase in risk would only require 112 abaloparatide users and 555 users of teriparatide (the active comparator).

Table 4: Sample size needed under different scenarios of incidence and HR, with matching 1:5 (abaloparatide:teriparatide)

Assumed incidence*	1%		2%		3%		4%	
Non-inferiority margin based on the HR	ABL	Comp	ABL	Comp	ABL	Comp	ABL	Comp
3.0	436	2,178	220	1,096	148	735	112	555
2.5	726	3,625	365	1,822	245	1,221	185	920
2.0	1,521	7,603	764	3,815	511	2,553	385	1,921
1.8	2,307	11,533	1,157	5,784	774	3,867	582	2,909
1.6	3,978	19,886	1,994	9,966	1,332	6,660	1,002	5,006
1.5	5,639	28,192	2,825	14,124	1,887	9,434	1,418	7,090
1.4	8,672	43,356	4,343	21,713	2,900	14,498	2,179	10,891
1.2	33,576	167,880	16,802	84,008	11,211	56,051	8,415	42,073

CI=confidence interval; Comp=comparator; CV=cardiovascular; HR=hazard ratio; ABL=abaloparatide
Note: For the non-inferiority design it is the number of abaloparatide and teriparatide users needed to obtain a 1-sided alpha risk of 0.025 with 90% power in a 1:5 (abaloparatide:teriparatide) matched cohort analysis for different scenarios of incidence of CV events at the end of 18 months and HR, where the true risk is 1.0 and 0% dropout. Stata 15 ('artsurv' command) was used for sample size calculations (28).

*Per 100 person-years.

It is estimated that to achieve non-inferiority margin of 3, the smallest sample size of 112 abaloparatide users would take one year of the study whilst it would take until year 3 to achieve the sample size of 436 abaloparatide users. Occurrence of the events of interest in the databases will be monitored at prespecified interim report time points. These data were based on:

- The number of patients expected from each country was assessed using an evaluation of epidemiologic data and the number of patients treated with the anabolic agent teriparatide.
- The assumption that local reimbursement criteria will allow the use of abaloparatide in the indicated population.

9.6 Data management

Due to the different database characteristics and coding schemes, it is not possible to use 1 single data extraction algorithm for all the databases.

Therefore, all databases will have been mapped to the OMOP CDM. This enables the use of standardised analytics and tools across the network since the structure of the data and the

terminology system is harmonised. The OMOP CDM is developed and maintained by the OHDSI initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org.

9.6.1 Data elaboration

Analytical code for this study will be written in R. Each data partner will execute the study code against their database containing patient-level data and will then return the results set which will only contain aggregated data. The results from each of the contributing data sites will then be combined in tables and figures for the study report.

9.6.2 Missing data

Since the underlying data represent attended medical care, it is assumed that for medical history conditions / comorbidities to be collected for inclusion in the propensity score, the absence of a condition will be interpreted as an absence of the event. No high frequency of missing values is expected for most variables, with the possible exception of smoking and/or alcohol dependence, but this is unlikely to be differential between treatment cohorts.

9.7 Data analysis

The proposed comparative safety analysis aims to assess whether in women with OP at increased risk for fracture, treatment with abaloparatide is associated with an increased risk of CV events of MI, stroke, all-cause mortality (including CV death) and arrhythmia compared to users of teriparatide similar to the population for abaloparatide in Europe as per the indications of the EU SmPC and with similar baseline characteristics.

A description of the analytical approach is described in the SAP. Further details on data sources, concept codes for outcomes, exposure and covariates, category definitions, analyses, methods for handling confounding, and presentation of the study results will be provided in SAP. The SAP will be refined and finalised during the conduct of the study analyses.

9.7.1 Statistical elements

9.7.1.1 Data analysis of the descriptive study component

9.7.1.1.1 CV incidence rates

For the analysis which determines the IR of each CV event of interest for abaloparatide or teriparatide, the following calculation will be performed:

$$\text{IR of CV events of interest} = \frac{\text{number of new events (after index date) among patients in the study drug cohort}}{\text{number of exposed person} * \text{years at risk for the study drug cohort}}$$

Incidence rates and 95% CIs will be calculated for both study drug exposure cohorts (as defined in Section 9.3.1). These rates will be presented and reported annually, and the number of patients and person-years at risk will be cumulative. In the first interim report CV IRs will be reported after the first year following launch. Subsequently, in the second and final reports, CV IRs will include both newly identified patients in addition to all patients identified in the first interim report.

9.7.1.1.2 Stratified CV incidence rates

For both study drug exposure cohorts, the CV IRs and 95% CIs will be stratified by the variables presented in Section 9.3.3.2.

9.7.1.2 Comparative safety analyses

9.7.1.2.1 Propensity score matching

Propensity scores represent the probability that a given patient will receive the drug of interest based on baseline covariates. For each person in a cohort, we will calculate propensity scores using large-scale L1 regularised logistic regression (19).

Propensity score matching reduces confounding by indication by producing comparable groups of patients in terms of observed confounders.

Patients using abaloparatide will be matched to up to 5 users of teriparatide with a caliper width of 0.20 standard deviations (SDs) on the logit of the propensity score (29). Caliper matching is a strategy where only abaloparatide users with "comparable" matches are kept in the analysis, whilst those with matched controls outside of the pre-established level of SD are excluded to minimize confounding. This is state-of-the-art methodology to minimize confounding by indication in pharmacoepidemiology and has been shown to replicate findings from randomized controlled trials in different settings (30, 31), including CV studies (32). An active comparator new user study design approach will be used (33).

Both pre-match and post-match balance between the two treatment cohorts will be evaluated using standardised mean difference for each covariate category to ensure that propensity score matching is acceptable (i.e., the standardised mean difference on each covariate between abaloparatide and teriparatide of < 0.10). A difference ≥ 0.1 will indicate that there is an imbalance between the two treatments on the specific variable. In this scenario, the propensity score model will be re-specified and re-estimated and the balance will be rechecked. If this strategy fails, double -adjustment (i.e., further adjustment for imbalanced variables) to adjust for any potential imbalances after matching will be used, as recommended by Nguyen et. al. (34).

9.7.1.2.2 Survival analysis

The as-treated analysis will be conducted for the comparative safety evaluation, continuous exposure is assumed if the gap between two prescription fills was ≤ 30 days. The comparative safety evaluation will be performed for all abaloparatide and teriparatide patients eligible for this study, for patients in the two treatment cohorts before and after PS-matching, and for patients stratified by the variables described in Section 9.3.3.2. Observation period will be for up to 18 months while on treatment plus 30-day follow-up, or until their first study event, whichever came first. Time to first study event after the index date and within 30 days after the end of treatment will be analysed. Cox regression models conditioned on the propensity score strata/matching will be used to calculate HRs and 95% CIs for each of the safety endpoints (MI, stroke, CV death, all-cause mortality, arrhythmia, MACE-1, and MACE-2) according to drug exposure in the propensity-matched cohorts. The outcomes of death and CV death will also be analysed using Cox regression to check for competing risks.

Should an association between abaloparatide use and primary outcome (MACE-1) be identified (in either direction), cause-specific hazards from competing risk analyses will be calculated to assess the risk of the secondary outcomes of MI and stroke (35).

The proportionality of hazards will be tested in all the Cox regression models by plotting log-plots of the Nelson-Aalen estimates. Alternative models will be used in case of non-proportionality of hazards.

9.7.1.2.3 Meta-analysis

We will use a meta-analysis random effects model to pool individual HRs together. In the scenario where between-database heterogeneity is high, defined as I^2>40% (36), we will only report database-specific estimates separately.

9.7.1.3 Measures proposed to account for unobserved confounding.

9.7.1.3.1 Negative control outcomes

Propensity scores account for measured confounders, but allegedly can fail to adjust for unmeasured (not recorded) confounders. Hence, we will use negative control outcomes, which are events upon which the treatment and comparator are not expected to have an effect, to detect residual confounding.

The negative controls to be used in this analysis will be agreed in advance before comparative analyses are conducted. The list of potential negative control outcomes is provided in the SAP.

If more than 20% of negative control outcomes have statistically significant HR with a treatment, we will not report the results because it indicates we fail to account for residual confounding. If there are less than 20% of negative control outcomes with significant HRs with a treatment, we

will attenuate residual confounding using the empirical calibration to estimate the true association with the outcomes of interests (37).

9.7.1.3.2 Empirical calibration using negative control outcomes.

The obtained estimates from the analyses above will be used to empirically calibrate the HRs obtained from the primary propensity-matched analysis, as proposed by Schuemie et. al. (38). This will provide a readjusted risk estimate of comparative CV safety after accounting for unobserved confounding.

9.7.1.4 Sensitivity analyses

9.7.1.4.1 Impact of pre-index date period (baseline period)

Although we anticipate no variations in the duration of the baseline period before index date between the exposure cohorts (abaloparatide vs. teriparatide), we will perform a sensitivity analysis, where all covariates assessed during the one-year period before the index date will be used.

9.7.1.4.2 Impact of exposure time

A sensitivity analysis will use an intention-to-treat analysis, where patients will be followed in their respective cohort until first occurrence of CV event of interest, lost to follow-up, death, or end of the study period. The follow-up period will be a maximum of 19 months following the index date, regardless of exposure status, cessation, addition of another OP medication, stopping or switching. Further information is added in the SAP.

9.8 Quality control

This study has been designed and shall be implemented and reported in accordance with the Guidelines for good pharmacoepidemiology practices of the International Society for Pharmacoepidemiology (39), the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines(40), and with the ethical principles laid down in the Declaration of Helsinki.

This study is fulfilling the criteria of a “ENCePP study” and follows the “ENCePP Code of Conduct” (2018).

9.8.1 General database quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). It is expected that each data partner will run the OHDSI Data Quality Dashboard tool (https://github.com/OHDSI/DataQualityDashboard). This tool provides numerous checks relating to the conformance, completeness, and plausibility of the mapped data.

Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values (19). Each of these categories has one or more subcategories and are evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

9.8.2 Study-specific quality control

Each of the contributing databases will first run an OHDSI cohort diagnostics package to identify the exposure cohorts described above. The results will include a summary of codes from the concept sets that are observed in the database and a summary of the concepts that led to entry into particular study cohorts. It also includes a check for ´orphan concepts´, concepts observed in the database that are not included in a concept set of a cohort but perhaps should have been. This will help to inform a consideration of the validity of the exposure cohorts in each of the databases. Subsequently, a cohort diagnostics package will be run to assess the identification of outcomes and patient features in an analogous manner.

9.9 Limitations of the research methods

This study is non-interventional and as such has several important limitations.

9.9.1 Selection bias

Primary and secondary care data are collected as and when individuals visit their GP or hospital and therefore samples from these databases may over-represent less-healthy individuals. However, this study is restricted to postmenopausal women with OP, therefore, selection will be mitigated, since they will likely attend medical care on a semiregular basis and thus have similar amounts and types of data recorded.

9.9.2 Information bias

Information bias may occur by not correctly measuring exposure, outcomes, or covariates.

With regards to exposure, misclassification may occur due to the patient not fulfilling the prescription (primary non-adherence) or in relation with non-compliance. Hence, an overestimate of utilisation of abaloparatide or teriparatide medications can happen, however this would potentially lead to non-differential misclassification.

Lack of recording (i.e., incompleteness) of exposure and safety events may lead to misclassification of the variables. We will conduct harmonization exercises and use data quality dashboards to minimize these issues in the contributing data sources.

There is a lack of death data in DA Germany (<0.1% out of total patients in the database) and no death data in PharMetrics® Plus which is a limitation in mortality assessment in these databases. There will be a potential underestimation of MACE-1 and MACE-2 events. However, death on these medications is expected to be rare. As shown in the pivotal Phase 3 BA058-05-003 study, there were small numbers of death (3 each in placebo and abaloparatide, and 2 in teriparatide); none were attributable to the abaloparatide or teriparatide (41). No deaths were reported in abaloparatide in a study using the US FDA Adverse Event Reporting System (FAERS) data (42).

In the planned comparative safety analysis, the lack of death data in these data sources is expected to result in non-differential misclassification of the outcome in both study drugs. If the rate of death is similar among abaloparatide and teriparatide, then the hazard ratio will not be biased. If the rate of death is higher among abaloparatide than teriparatide, then the hazard ratio will be biased towards the null.

9.9.3 Confounding

Due to the observational design chosen, causality in the observed associations will not be established. Instead, associations between drug use and risks will be assessed. As confounding by indication will produce differences in baseline characteristics between abaloparatide and teriparatide users, the study will use several methods to deal with confounding:

- Restriction: comparative studies will be conducted only in persons in line with the Europe label to restrict the population to those who would be prescribed abaloparatide according to the label (i.e., teriparatide users with severe renal impairment will be excluded).
- Matching: for the comparative studies, the study will use propensity score matching to minimize confounding related to all observed key confounder.
- Adjustment: the study will adjust for all covariates that remain imbalanced (standardised mean difference >0.1) after propensity score matching.
- Sensitivity analysis: negative control outcome analyses will be used to identify any residual unobserved confounding in the propensity score matching analyses. If this analysis suggests the presence of relevant unresolved confounding, then empirical calibration will be used to minimize the impact of any resulting bias. These are detailed in the previous section (Section 9.7.1.3).

9.10 Other aspects

Not applicable

10 PROTECTION OF HUMAN SUBJECTS

This PASS is a non-interventional (observational) study in compliance with the definition of non-interventional study provided in the 2017 Guideline on Good Pharmacovigilance Practice (GVP): Module VIII – post-authorisation safety studies, revision 3 (EMA/813938/2011, Rev 3, 2017) and in the ICH guideline of Pharmacovigilance Planning (ICH, 2004)

This PASS will use secondary data collection and does not pose any risks for patients.

For this study, participants from 4 different countries will process individual data as collected in national electronic health record/claims databases in compliance with all applicable national and European regulation as well as with ethical and regulatory issues including those on privacy.

All of the databases used in this study are already used for pharmacoepidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to.

In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses will be run, which generate non-identifiable data with less information that will be pooled across databases.

The PASS was registered in the HMA-EMA Catalogues of real-world data sources and studies (EUPAS1000000613).

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE DRUG REACTIONS

According to the most recent guidelines for GVP (EMA/395730/2012 Rev 3) (EMA/813938/2011, Rev 3), there is no requirement for expedited reporting of adverse drug reactions from studies with secondary use of data (such as electronic health care databases), which consists of fully de-identified data. Therefore, it is not possible to assess the causality of individual cases.

There will be no reporting of adverse events/reactions for this study. The study outcomes will be provided in the study interim and final reports in aggregate tables.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Interim reports at year 1 and 2 including the descriptive statistics and the comparative safety analysis results (sample size achieved) of abaloparatide will be generated and reviewed. These reports will be submitted to EMA.

Further, dissemination activities will be undertaken including articles in scientific journals and presentations at conferences. Publications will be developed according to EU partner policies and authorship will be determined in accordance with the International Committee of Medical Journal Editors (ICMJE) guidelines.

In order to allow national competent authorities to review the results and interpretations to be published in advance, the MAH will communicate with the Agency and the competent authorities of the Member States where the product is authorised, the final manuscript of the article within 2 weeks after first acceptance for publication.

All interim and final study reports will be prepared in accordance with the Guidelines on Good Pharmacovigilance Practice – Module 8. All analytical code related to the generation of tables

and figures for this report will be available to the agency in an open repository (e.g., GitHub). A data steward will be named for each contributing institution, with access to the harmonised data used for the analyses. Both the analytical code and analysed data will be available to the Agency upon request as per ENCePP guidance on data access (https://www.encepp.eu/code_of_conduct/documents/Annex4_SharingData.pdf).

The draft study reports will first be reviewed by the study team and updated if needed. These updated draft study reports will then be sent to EMA.

Feedback from EMA will be incorporated in the following study report (interim or final). Upon finalisation, the final study report will also be uploaded to the HMA Catalogue registry.

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APPENDIX 1. LIST OF STAND-ALONE DOCUMENTS

None.

APPENDIX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: European non-interventional post-authorization safety study (PASS) to assess cardiovascular (CV) events and all-cause mortality in patients exposed to abaloparatide or teriparatide.

EU PAS Register® number:
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☐	☐	☒	
1.1.2 End of data collection[2]	☐	☐	☒	
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

The final timelines will depend on the date of the protocol approval

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7 & 8
2.1.1 Why the study is conducted? (e.g., to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.3
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☒	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g., cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.2
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7.1
3.4	Does the protocol specify measure(s) of association? (e.g., risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7.1
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g., adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2.1
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2.2
	4.2.2 Age and sex	☒	☐	☐	9.2.3
	4.2.3 Country of origin	☒	☐	☐	9.2.3
	4.2.4 Disease/indication	☒	☐	☐	9.2.3
	4.2.5 Duration of follow-up	☒	☐	☐	9.2.3
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	9.2.5 & 9.2.6

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g., operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☐	☒	☐	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.3.1
5.4 Is intensity of exposure addressed? (e.g., dose, duration)	☐	☒	☐	
5.5 Is exposure categorised based on biological mechanism of action and considering the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.3.1

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, use of validation substudy)	☐	☒	☐	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g., HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g., confounding by indication)	☒	☐	☐	9.9.3
7.2 Does the protocol address selection bias? (e.g., healthy user/adherer bias)	☒	☐	☐	9.9.1
7.3 Does the protocol address information bias? (e.g., misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9.2

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g., collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.3.3.2

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3.1
9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.2
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
9.2.2 Outcomes? (e.g., date of occurrence, multiple events, severity measures related to event)	☒	☐	☐	9.4
9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.4
9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.4 Is a linkage method between data sources described? (e.g., based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.1.1
10.4 Are stratified analyses included?	☒	☐	☐	9.7.1.1.2
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.1.2.1 & 9.7.1.3
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.9
10.7 Does the plan describe methods for managing missing data?	☒	☐	☐	9.6.2
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.9

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	10

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9.1
12.1.2 Information bias?	☒	☐	☐	9.9.2
12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9.3
12.2 Does the protocol discuss study feasibility? (e.g., study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☒	☐	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g., to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: _____

Date: dd/Month/year

Signature: _____