NCT #NCT04974723

Clinical Study Protocol

A Retrospective, Observational Cohort Study Evaluating the Effectiveness and Cardiovascular Safety of Abaloparatide in Postmenopausal Women New to Anabolic Therapies

This study will be conducted according to the protocol and in compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), Health Insurance Portability and Accountability Act (HIPAA) guidelines, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

Protocol Number:	BA058-05-028
Version Number:	Original
Version Date:	V1.0, 09 July 2021
IND Number:	N/A
NCT Number:	Requested
Active Ingredient:	Abaloparatide, a novel synthetic peptide analogue of PTHrP (human parathyroid hormone-related protein)
Country of Study:	United States of America
Sponsor:	Radius Health, Inc. (Radius) 22 Boston Wharf Road, 7th Floor Boston, Massachusetts 02210 United States of America Telephone: (617) 551-4700 Fax: (617) 551-4701
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Clinical Research Organization:	PRA Health Sciences

1. TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Term
ABL	Abaloparatide subcutaneous (abaloparatide-SC; TYMLOS®)
ACTIVE	Abaloparatide Comparator Trial in Vertebral Endpoints
ACTIVExtend	Abaloparatide Comparator Trial in Vertebral Endpoints extension study
AE	Adverse event
AT	As-Treated (analysis)
AVA	Anabolic Versus Antiresorptive
BMD	Bone mineral density
bpm	beats per minute
CCI	Charlson Comorbidity Index
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence interval
CMS	Centers for Medicare & Medicaid Services
CPT	Common Procedural Terminology
CQ	Case qualifying
CTX	C-telopeptides of type 1 collagen crosslinks
CV	Cardiovascular
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
CTX	C-telopeptides of type 1 collagen crosslinks
CV	Cardiovascular
CTX	C-telopeptides of type 1 collagen crosslinks
CV	Cardiovascular
EMA	European Medicines Agency

EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCPCS	Healthcare Common Procedure Coding System
HIPAA	Health Insurance Portability and Accountability Act
hPTHrP(1-34)	First 34 amino acids of human parathyroid hormone-related peptide
HR	Hazard ratio
HRQoL	Health-related quality of life
ICD	International Classification of Diseases
ICD-9	International Classification of Diseases, 9th Revision
ICD9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICD10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
ICH	International Council on Harmonisation
ICSR	Individual Case Safety Report
IOF	International Osteoporosis Foundation
IRB	Institutional review board
IRR	Incidence rate ratio
ITT	Intention-to-treat (analysis)
MACE	Major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
NDC	National Drug Code
NOF	National Osteoporosis Foundation
P1NP	Procollagen type 1 N-terminal propeptide
PS	Propensity score
PTD	Patient Transactional Dataset
SAS	Statistical Analysis Software
SC	Subcutaneous
SD	Standard deviation

SmPC	Summary of Product Characteristics
TPTD	Teriparatide subcutaneous (Forteo)
USA	United States of America
WHO	World Health Organization

2. PROTOCOL SYNOPSIS

Title:

A Retrospective, Observational Cohort Study Evaluating the Effectiveness and Cardiovascular Safety of Abaloparatide in Postmenopausal Women New to Anabolic Therapies

Name of Sponsor:

Radius Health, Inc. (Radius)

Reference Drug:

Teriparatide subcutaneous (TPTD; Forteo®)

Background and Rationale:

Osteoporosis is a highly prevalent systemic skeletal disorder characterized by compromised bone strength predisposing individuals to an increased risk of fractures. Anabolic drugs, which can add bone and potentially improve bone microarchitecture, have become available as an additional treatment options for individuals with osteoporosis. These anabolic drugs include teriparatide (TPTD; Forteo: Eli Lilly and Co., Indianapolis, IN, USA), a first-in-class anabolic agent that received United States of America (USA) Food and Drug Administration (FDA) approval in 2002, abaloparatide (ABL; TYMLOS: Radius Health, Inc., Boston, MA, USA), approved by the FDA in 2017 and romosozumab (Romo; Evenity: Amgen and UCB, Thousand Oaks, CA, USA), a humanized monoclonal antibody with dual action approved by the FDA in 2019. The FDA approval of ABL included consideration of results at 18 months from the landmark ACTIVE trial and the first 6 months of the ACTIVExtend trial, which demonstrated consistent significant and rapid reductions in the risk of vertebral and nonvertebral fractures regardless of age, years since menopause, presence or absence of previous fracture, and bone mineral density (BMD).

Research Question:

The purpose of the current study is to evaluate the real-world comparative effectiveness and cardiovascular safety of ABL compared with TPTD during the 18-month period after treatment initiation in propensity score (PS)-matched cohorts.

Objectives and Endpoints:

Objectives	Endpoints
Primary Objective: • To evaluate the effectiveness of ABL for the treatment of osteoporosis in postmenopausal women in the real-world healthcare setting in the USA compared with TPTD using the same cohort of PS-matched patients.	**Primary Endpoint:** • Time to the first incidence of nonvertebral fracture (hip, pelvis, shoulder, radius or ulna, wrist, femur, tibia or fibula, ankle) within the 18 months after treatment initiation.
Secondary Objective: • To evaluate the cardiovascular safety of ABL for the treatment of osteoporosis in postmenopausal women in the real-world healthcare setting in the USA compared with TPTD using the same cohort of PS-matched patients.	**Secondary Endpoints:** • Time to the first incidence of the composite endpoint of nonfatal MI, nonfatal stroke, or in-hospital cardiovascular death within the 18 months after treatment initiation and while still on therapy. • Time to the first incidence of the composite endpoint of nonfatal MI, nonfatal stroke, heart failure or in-hospital cardiovascular death within the 18 months after treatment initiation and while still on therapy.
Exploratory Objective: • To further evaluate the effectiveness and cardiovascular safety of ABL for the treatment of osteoporosis in postmenopausal women in the real-world healthcare setting in the USA compared with TPTD using the same cohort of PS-matched patients.	**Exploratory Endpoints:** <u>Efficacy</u> • Time to the first incidence of hip fracture within the 18 months after treatment initiation. <u>Safety</u> • Time to the first incidence of MI • Time to the first incidence of stroke • Time to the first incidence of -in-hospital cardiovascular death • Time to the first incidence of heart failure

Study Design:

This is a retrospective observational cohort study using healthcare administrative claims data from the USA.

Setting:
This study will use anonymized patient level data from PRA's Symphony Health Patient Source Integrated Dataverse (IDV) database. Data are routinely collected in healthcare encounters from all available healthcare sites (inpatient hospital, outpatient hospital, physician office, pharmacy, etc.) for all types of provided services including specialty, preventive care, and office-based treatments.

Study Population:

Patient Population:

The patients for inclusion in the study analyses will be identified based on the prescribed anabolic therapy filled (ABL or TPTD). The study intake period was chosen to coincide with the date of the FDA approval of ABL in the USA.

Data Sources:
This study will use anonymized patient claims data from the Symphony Health Patient Source IDV database including the enhanced hospital data.

Study Size:
This retrospective cohort study is expected to include a total of 16,000 patients; 8000 patients per treatment cohort (ABL or TPTD).

Data Analysis:
Comparison of the time to the first incidence of fracture or cardiovascular outcomes between the PS-matched treatment cohorts will be based on the 2-sided 95% confidence interval of hazard ratio between ABL versus TPTD from a Cox proportional hazards model in both the effectiveness and safety analyses, The Kaplan-Meier method will be used to estimate event rates. Log rank test p-value will be calculated. All analyses will be based on the index medication cohort (ABL or TPTD).

Milestones:
No interim analyses or reporting are planned.

3. RESPONSIBLE PARTIES

This study is sponsored by Radius Health, Inc.

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4. VERSION HISTORY

Version Date	Version Number	Change Log	Rationale for Change
09 July 2021	1.0	Not applicable.	Not applicable.

5. RESEARCH QUESTIONS, OBJECTIVES, AND ENDPOINTS

5.1. Research Questions

The purpose of the current study is to evaluate the real-world effectiveness and cardiovascular safety of abaloparatide (ABL) compared with teriparatide (TPTD) for the treatment of osteoporosis in postmenopausal women during the 18-month period after treatment initiation in propensity score (PS)matched cohorts.

5.2. Objectives and Endpoints

Objectives	Endpoints
Primary Objective: • To evaluate the effectiveness of ABL for the treatment of osteoporosis in postmenopausal women in the real-world healthcare setting in the United States of America (USA) compared with TPTD using the same cohort of propensity score (PS)-matched patients.	**Primary Endpoint:** • Time to the first incidence of nonvertebral fracture (hip, pelvis, shoulder, radius or ulna, wrist, femur, tibia or fibula, ankle) within the 18 months after treatment initiation.
Secondary Objective: • To evaluate the cardiovascular safety of ABL for the treatment of osteoporosis in postmenopausal women in the real-world healthcare setting in the USA compared with TPTD using the same cohort of PS-matched patients.	**Secondary Endpoints:** • Time to the first incidence of the composite endpoint of nonfatal MI, nonfatal stroke, or in-hospital cardiovascular death within the 18 months after treatment initiation and while still on therapy. • Time to the first incidence of the composite endpoint of nonfatal MI, nonfatal stroke, heart failure or in-hospital cardiovascular death within the 18 months after treatment initiation and while still on therapy.
Exploratory Objective: • To further evaluate the effectiveness and cardiovascular safety of ABL for the treatment of osteoporosis in postmenopausal women in the real-world healthcare setting in the USA compared with TPTD using the same cohort of PS-matched patients.	**Exploratory Endpoints:** <u>Efficacy</u> • Time to the first incidence of hip fracture within the 18 months after treatment initiation. <u>Safety</u> • Time to the first incidence of MI • Time to the first incidence of stroke • Time to the first incidence of in-hospital cardiovascular death • Time to the first incidence of heart failure

5.3. Justification of Objectives and Endpoints

Comparative effectiveness for PS-matched ABL-treated patients versus TPTD-treated patients will be evaluated for nonvertebral fracture and hip fracture using a claims-based algorithm (Wright et al, 2019). Evaluation will be limited to nonvertebral fractures given the evidence requirement from regulatory authorities in the European Union (EU). Hip fractures, an important type of nonvertebral fractures that are associated with a greater disease burden including functional decline, loss of independence, and increased risk of mortality, will also be evaluated. Although hip fractures account for 14% of all fractures, they constitute 72% of the cost of osteoporotic-related fracture in the USA (Burge et al, 2007; Gold et al, 2019; Kochanek et al, 2019). The ACTIVE study was not sufficiently powered to demonstrate a significant reduction in hip fracture, but an observational study reported a 45% reduction in hip fracture for patients treated with TPTD (Burge et al, 2017). Evaluation of vertebral fracture incidence will not be carried out given the limitation of healthcare claims data that would only capture clinical vertebral fractures (ie, those corresponding to a healthcare encounter). Subgroup analyses will be conducted based on osteoporosis treatment history, given the variation in response to anabolic treatment by osteoporosis treatment history, and in patients considered to be at high risk for fractures.

Comparative cardiovascular safety for PS-matched ABL-treated patients versus TPTD-treated patients will be evaluated based on time to the first incidence of the composite endpoint of nonfatal myocardial infarction (MI), nonfatal stroke, and in-hospital cardiovascular death within the 18 months after treatment initiation while still on therapy. The International Classification of Diseases, 10th Revision, Clinical modification (ICD-10-CM) codes for MI, stroke, and heart failure from the Food and Drug Administration (FDA) Mini-Sentinel database (FDA, 2021) will be used as a guide for event identification with modifications to ensure that relevant endpoints are captured (Appendix 4). Published results from a validation study of the MI codes used in the Mini-Sentinel database demonstrated a positive predictive value of 86% (Cutrona et al, 2013). For evaluation of mortality, hospital discharge status will be used. It is important to note that hospital claims do not specify the cause of death nor causal association with a specific medication. A previously validated claims-based algorithm will be used to derive in-hospital cardiovascular death (indirect approach 2, Xie et al, 2018). Compared to a previously published fatal MI and stroke method (Ritchey et al, 2017), the algorithm we adopted has higher sensitivity while maintaining high specificity. The net reclassification index is improved.

6. BACKGROUND AND RATIONALE

6.1. Disease Background

Osteoporosis is a highly prevalent systemic skeletal disorder characterized by low bone mineral density (BMD), decreased bone strength, and microarchitectural deterioration of bone tissue that leads to enhanced fragility and increased risk of fractures (Rizzoli et al, 2001). The fractures associated with the greatest morbidity and mortality, as well as an economic burden to society, together make up the clinically significant and medically relevant group termed major osteoporotic fractures. According to the International Osteoporosis Foundation (IOF), approximately 10 million Americans have osteoporosis and 44 million more have low bone mass (osteopenia) (IOF, 2020). In the USA, there are an estimated 2 million osteoporotic fractures annually (Litwic et al, 2014). At the age of 50, a woman in the USA has a lifetime risk of approximately 50% for incurring osteoporotic fractures (Cosman et al, 2014). As the population ages, the number of osteoporotic fractures is certain to increase in both men and women by more than 3-fold over the next 50 years (World Health Organization [WHO] 2007).

One of the major public health problems associated with osteoporosis is its association with low-energy trauma or fragility fractures. Fragility fractures affect up to one-half of women and one-third of men over the age of 50 years and are often associated with low bone density (Cummings and Melton, 2002; Ross, 1996; Jones et al, 1994). Such fractures occur most commonly in the hip, spine, and wrist (Cummings and Melton, 2002; Tosteson et al 2001). Clinical studies have demonstrated that treatment of patients with fragility fractures can reduce the risk of future fractures (Delmas, 2002; Hochberg 2000). Thus, it is important that these patients not only receive treatment for the presenting fracture, but also treatment for the prevention of future fractures (Tosi and Lane, 1998; Rosier 2001).

Spinal fractures have also been associated with poor outcomes and high mortality rates (Suzuki et al, 2008). It has been reported that once a patient has sustained a vertebral fracture, the risk of a subsequent vertebral fracture increases by > 300% and the risk of a subsequent hip fracture increases by 200% (Black et al, 1999). Additional studies have shown that almost half of patients with a prior vertebral fracture will experience additional vertebral fractures within the next 3 years, many within the first year (Robinson et al, 2002; Lindsay et al, 2001). Patients who sustained a vertebral body fragility fracture had a prolonged course, which can lead to significant disability even 1 year later (Suzuki et al, 2008). Patients with a diagnosis of osteoporosis who have experienced any fracture have an 86% increase in their risk for another fracture (Kanis et al, 2004). With the severity of these implications, prevention of subsequent fractures has become a primary focus from a patient care and societal standpoint.

Major osteoporotic fractures (those of the wrist, shoulder, hip, and clinical spine) account for 94% of the fracture risk for women with low or minimal trauma (Ensrud et al, 2016). Major osteoporotic fractures contribute to accumulated frailty such that the Frailty Index is significantly higher in those elderly women who have experienced a major osteoporotic fracture. As a result, these women have worsening frailty and greater morbidity after a major osteoporotic fracture (Li et al, 2016). The Frailty Index was associated with a predicted increase in the risk of falls, fractures, death, and overnight hospitalizations (Li et al, 2014). Consequently, prevention of clinically significant and medically relevant major osteoporotic fractures has the potential to reduce health care costs, and reduce the risk of falls, fractures, hospitalizations, and death as well as benefit postmenopausal women based on reduced frailty.

Suffering a major osteoporotic fracture substantially increases the risk of subsequent fractures (Burshell et al, 2010), and this risk is highest in the first few years after a fracture. There is strong evidence demonstrating that after hospital discharge, patients with an osteoporotic fracture face higher morbidity, subsequent fractures, and increased mortality (Nazrun et al, 2014). Of the estimated 2 million annual osteoporotic fractures in the USA, the most common fracture site is the distal radius where 640,000 cases were reported in 2001 alone (Litwic et al, 2014). These incident fractures represent an event that is associated with a highly elevated risk of a subsequent major osteoporotic fracture within the next 1 to 2 years (Barrett-Connor et al, 2009; Chen et al, 2013). Anabolic therapy is often recommended for patients at a high risk of future fracture, including patients with recent fracture and patients with multiple fractures, but evidence for rapid protection of all-site fractures is lacking.

Previously, it has been observed that postmenopausal women with osteoporosis have a 4-fold higher increased risk for cardiovascular events compared with postmenopausal women without osteoporosis (Tankó et al, 2005). Additionally, Tanko et al reported that postmenopausal women with a low BMD value, bone loss, and presence of previous fracture have an increased mortality due to cardiovascular causes. The inverse relationship between bone mass and coronary heart disease risk in women found in this study is supported by reports that postmenopausal women with low BMD values or a greater degree of bone loss have a greater prevalence and severity of aortic calcification, a predictor of cardiovascular disease incidence and mortality. This inverse relationship was independent of age, education, smoking, alcohol, systolic blood pressure, lipids, diabetes, and menopausal history. The inverse relationship between the metacarpal cortical area and the incidence of coronary heart disease observed in women might suggest that efforts to reduce the risk of osteoporosis may decrease the risk of coronary disease in women (Samelson et al, 2004).

6.2. Currently Available Treatment Options

Treatment options for osteoporosis that are currently available in the EU can be divided into 2 broad categories:

- Antiresorptives: bisphosphonates and denosumab
- Anabolics: TPTD and romosozumab

Most of the antiresorptive products provide only a moderate rate of increase in BMD and require several years of treatment to reach their fracture reduction benefit. Given that ABL is an anabolic, only ABL and the approved anabolics – TPTD and romosozumab – are discussed further herein.

6.2.1. Teriparatide

Teriparatide [rhPTH(1-34)] is closely related to ABL and among its approved European Medicines Agency (EMA) indications is the treatment of osteoporosis in postmenopausal women (and men) at increased risk of fracture. This approval was based on a significant reduction in the incidence of vertebral and nonvertebral fractures.

Clinical data supporting anabolic the effects of TPTD include the demonstration of elevated levels of the bone formation marker procollagen type 1 N-terminal propeptide (P1NP) and the bone resorption marker C-telopeptides- of type 1 collagen crosslinks (CTX) in the Anabolic Versus Antiresorptive (AVA) study in patients receiving TPTD at 20 µg SC daily (Dempster et al, 2016). Levels increased significantly starting at 1 and 3 months, and continued to rise through 6 months, and were greater for P1NP suggesting evidence for a "net anabolic effect".

In the AVA study, using quadruple labeling, TPTD increased from baseline all forms of bone formation (modeling, remodeling, and overflow modeling bone formation) in the cancellous and endocortical bone envelopes and modeling-based bone formation was seen in the periosteum (Dempster et al, 2018).

The Summary of Product Characteristics (SmPC) for teriparatide shows that nausea, pain in limb, headache, and dizziness are the most commonly reported adverse reactions. For cardiovascular adverse events (AEs), palpitations are noted to be common, but tachycardia is uncommon. Orthostatic hypotension is included in the Warnings and Precautions section. Despite the occurrence of these class-effect AEs, there is no evidence of an increase in major cardiovascular AEs for TPTD.

6.2.2. Romosozumab

Romosozumab, a monoclonal antibody that acts as a sclerostin inhibitor. was approved in 2019 for the treatment of osteoporosis in postmenopausal women at high risk of fracture. Nonclinical and clinical studies have demonstrated a mixed anabolic/antiresorptive effect on bone. Romosozumab was approved based on the results from 2 randomized controlled pivotal studies in 2 different populations with different levels of fracture risk. In the ARCH study (Saag et al, 2017), romosozumab demonstrated a statistically significant reduction in fracture rate at 12 months compared with alendronate, including a reduction in the rate of nonvertebral fractures. However, in the placebo-controlled FRAME study (Cosman et al, 2016), while the results were positive for the primary endpoint of new vertebral fractures, the rate of improvement of nonvertebral fractures did not reach statistical significance.

Clinical data supporting the anabolic effects of romosozumab include demonstration of a rapid increase in bone formation demonstrated by P1NP levels peaking at 1 month, but then declining to the baseline level by Month 6 in both the FRAME and ARCH studies. In addition, there was evidence of suppression of bone resorption, as CTX levels rapidly decreased by 50% from baseline at 1 month and remained at that level throughout the remaining 12 months of treatment.

The histomorphometry completed on patients in the FRAME study at 2 months after quadruple label staining demonstrated a doubling from baseline of dynamic bone formation indices but bone resorption was halved suggesting this initial gain was modelling based; biopsies at 12 months showed that the parameters of dynamic bone formation were decreased; there was no significant evidence for cortical porosity (Chavassieux et al, 2019).

In the SmPC, the use of romosozumab is contraindicated in patients with a history of MI or stroke. In randomized controlled clinical studies, an increase in serious cardiovascular events (MI and stroke) was observed in subjects treated with romosozumab compared with control subjects.

6.2.3. Abaloparatide

Abaloparatide is a chemically synthesized analog of the first 34 amino acids of human parathyroid hormone-related peptide [hPTHrP(1-34)] that is anabolic in bone. Secondary pharmacological effects of ABL include transient and reversible increases in heart rate after injection, with associated AEs of palpitations and tachycardia observed in the pivotal clinical study. A post-hoc analysis was performed to examine the effects of treatment on heart rate, blood pressure, and cardiovascular-related AEs, including MACE with or without heart failure in the ACTIVE/ACTIVExtend study (Cosman et al, 2020). ABL and TPTD transiently increased heart rate relative to placebo. After the first dose, the mean (SD) change in heart rate from before treatment to 1 hour after treatment was 7.9 (8.5) bpm for ABL, 5.3 (7.5) bpm for TPTD, and 1.2 (7.1) bpm for placebo. A similar pattern was observed over subsequent visits. The corresponding change in mean supine systolic and diastolic blood pressure 1 hour after treatment was -2.7/-3.6 mmHg for ABL, -2.0/-3.6 mmHg for TPTD, and -1.5/-2.3 mmHg for placebo. The percentage of participants with serious cardiac AEs was similar across the treatment groups (0.9% and 1.0%). In a post-hoc analysis, the percentage of participants with MACE during the ACTIVE study was 0.5% in the ABL group, 0.6% in the TPTD group, and 1.2% in the placebo group; MACE + heart failure increased the proportion in the placebo group to 1.7%. Time-to-first incidence of MACE + heart failure was significantly longer for ABL compared with placebo ($p = 0.02$) and for TPTD compared with placebo ($p = 0.04$; Cosman et al, 2020). During the 2-year ACTIVExtend period, the incidence of MACE, with or without heart failure, was similar between the placebo/alendronate and ABL/alendronate groups leading to the conclusion that ABL was associated with transient increases in heart rate and small decreases in blood pressure in postmenopausal women with osteoporosis, with no increase in risk of serious cardiac AEs, MACE, or heart failure.

No published epidemiological studies have examined the cardiovascular risk associated with transitory, intermittent increases in heart rate due to an external intervention, as is the case with ABL administration, in the general population and in the target population of postmenopausal women. A review of data on the long-term effects of TPTD, which has a similar mechanism of action to ABL, and whose administration is associated with a similar (although slightly less pronounced) increase in heart rate, follow-up study of the Fracture Prevention Trial of TPTD versus placebo (N = 1262), did not show a discernible increase in cardiovascular disease after 5 years (Tashjian et al, 2006; Prince et al, 2005).

6.3. Study Rationale

Currently, no published studies on the comparative effectiveness or cardiovascular safety of ABL versus TPTD in a real-world setting are available (Fuggle et al, 2020). There are also no real-world data on the cardiovascular safety of these osteoanabolic agents in this patient population. In an earlier study, Radius used data from claims and electronic medical records to characterize patients new to ABL relative to patients new to TPTD. Results from that study were previously reported and the differences in patient characteristics in the real-world setting were noted when compared with the characteristics of patients in clinical studies (Imel et al, 2020). Furthermore, patients new to ABL treatment were similar in their disease characteristics to patients on TPTD. This observation reflects comparable market access to the 2 anabolic therapies in addition to an equivalence in prescribing recommendations based on clinical practice guidelines (Camacho et al, 2020).

Previously, Radius completed an analysis of Symphony Health Patient Source administrative claims data for evaluation of the market dynamics for osteoporosis treatments (Williams et al, 2019). The purpose of that study was to characterize patients new to anabolic treatment in the real-world setting and to evaluate incidence of fractures following treatment initiation. Baseline cardiovascular risk factors (ie, dyslipidemia, hypertension, diabetes, and obesity), disease history and cardiovascular events before and after treatment initiation were evaluated as exploratory analyses. Because the study started shortly after the launch of ABL (TYMLOS), limited longitudinal data were available to assess impact of treatment on fracture outcomes. Furthermore, the data capture rate for inpatient events was low (only 25% of inpatient events were captured). The current protocol incorporates the recommendations received from several national scientific advisory meetings in the EU to expand data scope and further evaluate the real-world comparative effectiveness and comparative cardiovascular safety of ABL versus TPTD. First, additional real-world data have been accumulated leading to a larger number of evaluable patients with a longer longitudinal data availability. Second, we have secured access to the enhanced hospital data through PRA Health Sciences, which provide access to 60% of inpatient events. Furthermore, mortality data, which were previously not available, can now be determined using hospital discharge records. A validated cardiovascular mortality algorithm (Xie et al, 2018) will be used to derive in-hospital cardiovascular mortality Both in-hospital cardiovascular mortality and all-causes mortality will be included.

The purpose of the current study is to evaluate the real-world comparative effectiveness and comparative cardiovascular safety of ABL versus TPTD during the 18-month period after treatment initiation in PS matched cohorts.

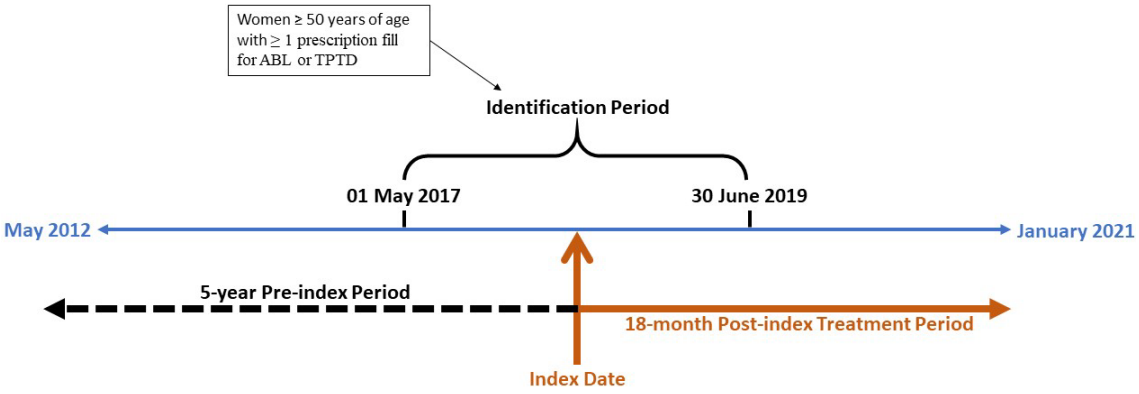
This study will be conducted by PRA Health Sciences using this prespecified protocol and statistical analysis plan. In the absence of randomization, this observational study will use propensity score (PS) matching for comparative evaluation of safety in addition to effectiveness outcomes. Further quality control work has been performed on the data including the assignment of codes. The study has reasonable power to show comparable effectiveness and safety profile between the 2 active treatment arms.

7. RESEARCH METHODS

7.1. Study Design

This will be a retrospective observational study using administrative data for the period from May 2012 to January 2021. The most recently available data at the time of data extraction will be used. This study will use anonymized patient claims data from PRA's Symphony Health Patient Source Integrated Dataverse (IDV) database with the inclusion of enhanced hospital data, which are claims and remittance from the inpatient hospital setting and proprietary Patient Transactional Dataset (PTD) claims and prescription data, to apply the inclusion/exclusion criteria for patient selection (see Section 7.4.1) to form the data set.

Figure 1 Study Design Schematic



ABL= abaloparatide; TPTD = teriparatide.
The **Identification Period** is the period of time during which subjects will be identified based on their index date (01 May 2017 to 30 June 2019).
The **Index Date** is the date on which the subject filed their first claim for a prescription for either ABL or TPTD during the identification period.
The **Pre-index Period** consists of the 5 years before the Index Date during which medical history was available for the subject.
The **Post-index Treatment Period** consists of the 18 months plus 30 days follow-up after the initiation of treatment with anabolic drug (ABL or TPTD) on the index date and continuing for the duration of treatment.

Treatment Cohorts

This is a real-world observational study. Treatments will not be assigned. Instead, cohorts are defined as follows:

- **Abaloparatide Cohort:** Patients who filled ≥ 1 prescription for ABL (TYMLOS) as their index medication during the identification period.

- **Teriparatide Cohort:** Patients who filled ≥ 1 prescription for TPTD (Forteo) as their index medication during the identification period.

Evaluation Period

The date of the first claim for either ABL or TPTD during the identification period (between May 1, 2017 and June 30, 2019) will be considered the index date.

- The medication received on the index date will be considered the index medication.
- Treatment duration may continue for up to 18 months (540 days) after the index date.
- The evaluation of outcomes will start immediately after treatment initiation and will continue for 18 months after the index date for both effectiveness and cardiovascular safety evaluation regardless of the drug possession gap between any 2 prescription fills.

Primary Analyses

- The primary effectiveness analysis will be an Intention-to-Treat (ITT) analysis.
- The primary safety analysis will be an As-Treated (AT) analysis.

Estimated Sample Size

Between May 2017 and June 2019, a total of 16,482 unique female patients ≥ 50 years of age treated with ABL and 45,350 unique patients ≥ 50 years of age treated with TPTD have been identified in the Symphony database. After applying inclusion/exclusion criteria, the final number of patients will be determined through PS matching. Based on previous studies, it is estimated that approximately 8,000 matched patients will be included in each cohort.

[redacted]

7.1.1. Rationale for the Current Study Design

Currently, there are no published studies on the effectiveness of ABL in the real-world setting. Furthermore, neither the comparative effectiveness nor comparative safety of ABL versus TPTD have been previously reported. In addition to clinical outcomes evaluated in randomized controlled studies, real-world effectiveness data are important in guiding treatment decisions. An evaluation of real-world effectiveness will provide data on a broader population of patients beyond the patient population included in the ACTIVE trial. Romosozumab is excluded from this study because of its association with an increased risk of cardiovascular events.

7.1.2. Strengths of the Study Design

The methodology for the current study design has several strengths:

- Data are from multiple payers and geographically diverse settings across the USA, and the PRA IDV data captures over 90% of pharmacy claims in the USA. The prescription claims are for prescriptions filled not just prescriptions written. As such, the findings from the study are expected to have a high generalizability.

- A claims-based algorithm, which has a high specificity and has been shown to have over 90% accuracy in previous studies, will be used (Wright et al, 2019).

- Although this is not a randomized study, PS-matching will be used to define study cohorts and provide confidence that the 2 cohorts were comparable in their probability to receive and benefit from treatment. Patients will be matched on all indicators of disease severity and fracture risk, including fracture and treatment history as per evidence-based clinical practice guidelines (Camacho et al., 2020). Furthermore, patients will also be matched on conditions associated with increased risk of fall and the requirement for treatments associated with poor bone health or quality.

7.1.3. Limitations of the Study Design

There are several limitations associated with the design of the current study:

- The data source is administrative claims data, which are not collected for research purposes. Administrative claims data have inherent limitations including coding errors, inconsistencies, underestimation, overestimation, or incomplete diagnoses data. The current study, however, will use a claims-based algorithm to identify case qualifying (CQ) fragility fractures associated with osteoporosis. Furthermore, any misclassification of fractures is nondifferential between the treatment groups being compared and should not affect the results.
- Claims-based studies include potential inaccuracies related to the use of prescription medications. The prescription claim is for the date of first fill and not the date of first use of the medication, so the assumption is that these are the same date.

- Detailed clinical data such as BMD T-scores or the presence of other risk factors (eg, family history, smoking status, alcohol intake) associated with disease severity and increased future fracture risk are not available and, therefore, no adjustments have been made for these factors.
- Only deaths recorded on the hospital discharge status are available for the derivation of cardiovascular death in this study. The current study, however, will use a claims-based algorithm to identify deaths that are likely to be caused by cardiovascular events. Furthermore, any misclassification of deaths is nondifferential between the treatment groups being compared and should not bias the results.

The comparative evaluation of treatment options is ideally done within the controlled clinical study setting. The current study is observational, and treatments are not assigned. As such, randomization is not possible. Although this is not a randomized study, PS matching will be used to define the study cohorts and provide confidence that the 2 treatment groups are comparable in their probability to receive and benefit from treatment. Patients will be matched on all indicators of disease severity and fracture risk including prior disease and treatment history. Furthermore, patients will also be matched on history of falls as well as comorbid conditions and concomitant medications associated with increased fall risk or with bone quality and strength. While several comorbidities were initially considered, some measures were ultimately not included in the end due to lack of available data. This includes duodenitis. Lastly, there could be residual confounding despite matching. The study is planned as an intention-to-treat (ITT) analysis for effectiveness evaluation and as-treated (AT) analysis for safety evaluation with additional consideration for duration of treatment exposure using sensitivity analyses on various length of observed treatment duration for the study cohorts. Interpretation is limited by the variable length of follow-up.

7.1.4. Generalizability

All patients will be required to have a total of 12 months of pre-index medical and prescription data. This may result in a study population that is less healthy with a higher incidence of fracture compared with that reported in ACTIVE. Regardless, this selection bias is not likely to differentially affect the 2 treatment cohorts. Results of the study are expected to be generalizable to the population of managed care enrollees including commercial and Medicare Advantage members. Regardless of this limitation, the data are representative of a broad population of patients from multiple payers and are geographically diverse across the USA. The study will provide additional information on real-world use and outcomes in patients new to treatment with ABL outside of the clinical study setting.

7.2. Setting

This study will use anonymized patient claims data from PRA (Symphony Health) IDV database. Data are routinely collected in healthcare encounters from all available healthcare sites (inpatient hospital, outpatient hospital, physician's office, etc.) for all types of provided services including specialty, preventive care, and office-based treatments.

The rationale for the study population and the generalizability of the results of these analyses to the general population of postmenopausal women with osteoporosis are discussed in Section 7.4.2.

This is a retrospective observational study evaluating real-world data and, therefore, there are no assigned study visits. The study uses a convenience sample. Patients in the Symphony database who meet the study inclusion/exclusion criteria (Table 1 and Table 2) will be included in the analyses.

7.3. Duration of Subject Participation

Because this is a retrospective claims-based cohort study, subjects included in the analyses will not actively participate in the study and no study visits will be required. The study will use anonymized patient data.

Both effectiveness and cardiovascular safety outcomes will be assessed for patients with 18 months of follow-up data from their index date.

7.4. Study Population

7.4.1. Subject Selection Criteria

Table 1details the inclusion criteria and Table 2 provides the exclusion criteria for this study.

Table 1 Inclusion Criteria

Criterion	Details	Order of Application	Assessment Window	Code Type	Diagnosis Position	Applied to Study Populations	Varied for Sensitivity	Source for Algorithm
Women	Sex female	Before selection of the index date	Any time	NA	NA	Yes	No	NA
Age: ≥ 50 years	≥ 50 years of age	Before selection of the index date	[0, 0]	NA	NA	Yes	No	Proxy for postmenopausal
≥1 prescription fill for ABL or TPTD	between May 1, 2017 and June 30, 2019 (identification period)	Will determine the index date	May 1, 2017 and June 30, 2019	NDC	NA	Yes	Yes. Further restriction on various duration of treatment	NA
≥ 1 claim for medical or hospital visit and a pharmacy claim	in the 12 months before the index date	Before selection of the index date	0-12 months pre-index	NDC, ICD, HCPCS	Any	Yes	Yes	PRA proprietary algorithm to determine coverage

ABL = abaloparatide; NA= not applicable; NDC = National Drug Code; post-index = after the index date; pre-index = before the index treatment date; TPTD = teriparatide.

Table 2 Exclusion Criteria

Criterion	Details	Assessment Window	Code Type	Diagnosis Position	Applied to Study Populations	Varied for Sensitivity	Source for Algorithm
Paget's disease	Presence of ≥ 1 claim for Paget's disease	Pre-index	ICD	Any	Yes	No	NA
Malignancy	Presence of ≥ 1 claim except for nonmelanoma skin cancers, carcinoma in-situ of the cervix, ductal carcinoma in-situ of breast	Pre-index	ICD	Any	Yes	No	NA
Indicators of high disease burden and high risk of death	CCI > 10	Pre-index	ICD	Any	Yes	No	NA
With prior index anabolic treatment	Anabolic treatment includes ABL, TPTD and romosozumab	Pre-index	NDC and HCPCS	NA	Yes	No	NA
Switch to a different anabolic treatment after index	Anabolic treatment includes ABL, TPTD and romosozumab	Index-date to 18 months after	NDC and HCPCS	NA	Yes	No	NA

CCI = Charlson Comorbidity Index; ICD = International Classification of Diseases; NA= not applicable; pre-index = before the index treatment date; post-index = after the index date.

7.4.2. Discussion of Study Population

The study eligibility criteria are in alignment with the prescribing information in the FDA approved labels for both ABL and TPTD and include women with postmenopausal osteoporosis. Patients with secondary osteoporosis, Paget's disease, as well as those who would not be candidates for the anabolic drug due to high morbidity burden or high risk of mortality (ie, malignancies), are excluded. Patients with prior alendronate therapy will be included because almost half of the population of patients new to anabolic therapies have previously used bisphosphonates. Although the treatment guidelines suggest initiation of therapy with bone building agents followed by antiresorptive agents to maintain bone, market access criteria requiring step therapy and prior authorization for anabolic agents result in the use of anabolic agents later in the course of disease progression and severity (McClung et al, 2017; Tsourdi et al, 2017; Zanchetta et al, 2018). Limiting the study population to those without any prior therapy would significantly reduce the size of the study population. Therefore, subgroup analyses will be performed based on prior use of osteoporosis treatment. Furthermore, there is no evidence indicating diminished treatment response to anabolic therapy following alendronate use (Cosman et al, 2017; Langdahl et al, 2018). As such the study criteria provide a suitable population for evaluation of the effectiveness and cardiovascular safety of ABL without compromising sample size yet minimizing potential selection biases.

7.5. Data Sources

This study will use anonymized patient level data from PRA's Symphony Health IDV database, including the enhanced hospital data. PRA's IDV database is a large nationally representative claims-based database. The database cross-sectionally covers over 80% of the population in the USA (approximately 300 million lives) annually. It includes claims submitted to all payer types, including commercial plans, Medicare, and Medicaid. In terms of the pharmacy claims, it captures approximately 92% of the retail and 65% specialty pharmacy claims, and approximately 68% of mail order claims. For medical claims, it covers approximately 60% of professional claims in an outpatient setting. Medical claims are open unadjudicated claims. Mortality data recorded on the hospital (medical facility) discharge status covers about 1/3 of the total death records According to National Center for Health Statistics data published on CDC wonder (CDC, 2021), 35% total deaths in 2019 happened at medical facility which includes hospital inpatient, outpatient or emergency room, death on arrival or unknow status. This number is slightly high (37%) for cardiovascular death (cause of death is I00 to I99 in ICD-10). For women at age 50, 54% percentage of cardiovascular death occurred in medical facilities. The data are de-identified, in compliance with Health Insurance Portability and Accountability Act (HIPAA) guidelines, with stable unique identifiers to allow for longitudinal tracking over time. The terms of the Research Exception provisions of the Privacy Rule, 45 Code of Federal Regulations (CFR) Part 164.514(e) exempts Institutional Review Board (IRB) approval for this nonexperimental study, which is fully HIPAA compliant.

Table 3 summarizes the calendar time range used to ascertain cohort entry (index date), as well as the calendar time range of data available for pre-index- assessment windows and post-index follow up (study period). The data source name and version are identified, as well as any sampling criteria applied (for example, the data cut only includes patients with a diagnosis of diabetes). If data linkage is involved, provide a citation or an appendix with description of the linkage (how, performance characteristics).

All individual data will be de-identified and signed data license agreements will be in place for all data sources.

Table 3 Metadata About Data Source and Software

Data Sources:	PRA (Symphony Health's) Integrated Dataverse (IDV) database.
Study Period:	May 1, 2012 to January 31, 2021
Eligible Cohort Entry Period:	May 1, 2017 to June 30, 2019
Data Extraction Date/Version:	June – 2021 via a single data pull
Data Sampling/ Extraction Criteria:	Refer to **Section 7: Research Methods** for study design, treatment cohorts, evaluation periods, and subject selection criteria.
Types of Data:	Medical, hospital and prescription claims data.
Data Linkage:	No data linkage will be required.
Data Conversion:	No data conversion will be required.
Software to Create Study Population:	[redacted] software used to connect to the Cloudera Hadoop CDH 7.1.4-1 database for data extraction. R software might be used for propensity score matching.

7.6. Variables for Data Extraction

The endpoints to be assessed in this study are provided in Section 5.2.

7.6.1. Demographics and Baseline Variables

Potential confounding variables include the following:

- Demographic variables (age, race/ethnicity if available)
- Insurance information (commercial, Medicare, Other)
- Patient geographic region (majority coverage includes West, South, Northeast, and Midwest)
- ABL and TPTD prescriber physician's specialty (endocrinology, rheumatology, surgery, family medicine, internal medicine, nursing related, obstetric
- Index date year quarter

7.6.2. Risk Factors

Conditions associated with increased risk of fractures or falls (Camacho et al, 2020), including pre-index fracture history, for which data are available in administrative claims, will be assessed by the presence of ICD codes in the claims database. History of co-morbidities associated with an increased risk of falls and/or fractures, as well as those conditions associated with poor bone health, will be assessed (see Section 7.6.3 for the list of co-morbidities).

Data for medical history associated with a high risk of cardiovascular events will also be extracted: MI, stroke, and heart failure.

7.6.3. Co-morbidities

Known co-morbidities identified in the target patient population that will be included in this retrospective cohort study are:

- **Comorbidities that increase the risk of fall:** prior history of any stroke, mobility impairments, vision impairments, hearing impairments, Parkinson's disease, muscle atrophy, muscle weakness, or sarcopenia.
- **Comorbidities that lengthen healing time:** diabetes, liver disease, or renal disease.
- **Other comorbidities associated with an increased risk of fractures or requiring treatment associated with an increased fracture risk:** hypertension, dyslipidemia, arthritis, respiratory diseases including asthma and chronic obstructive pulmonary disease, depression, anxiety, sleep disorders, cardiovascular disease, hypothyroidism, obesity, or gastrointestinal disorders.

7.6.4. Osteoporosis Treatment History

Pharmacy claim for previous use of any of the following medications:

- Bisphosphonates (ie, alendronate, ibandronate, risedronate, or zoledronate)
- Denosumab
- Oral glucocorticoids
- Hormone replacement therapy

7.6.5. Concomitant Medications

Concomitant osteoporosis medications expected to be used in the target patient population include the following:

- Bisphosphonates (ie, alendronate, ibandronate, risedronate, zoledronate)
- Denosumab
- Hormone replacement therapy

7.6.6. Anabolic Drug Exposure

Cohort anabolic drug exposure is defined as a prescription filled for either abaloparatide (ABL cohort) or teriparatide (TPTD cohort). Exposure will be determined using pharmacy claims data in the NDC Codes and HCPCS Codes for Medications. For a list of codes please see Appendix 5.

7.6.7. Outcomes

Both effectiveness and cardiovascular safety outcomes will be assessed for patients with 18 months of follow-up data after their index date. Cardiovascular safety outcomes will be evaluated during the treatment period which is from index date to the last prescription anabolic drug possessed within the 18 months after the index date, regardless of the anabolic drug possession gap between any 2 prescription fills.

7.6.7.1. Evaluation of Effectiveness

A claims-based algorithm with high specificity for fracture site developed by Wright et al (Wright et al, 2019) will be used to identify osteoporosis-related fractures (see Appendix 2). Case qualifying (CQ) fractures are those identified during an inpatient hospital stay, in any position on the medical claim, or in an outpatient setting accompanied by a fracture repair procedure code. Validation of this algorithm was done using International Classification of Diseases, 9th Revision (ICD-9) codes before the Healthcare System in the USA switched to the ICD-10 system. In a separate study, Wright et al mapped the ICD-9 codes to ICD-10 codes in an evaluation of hip fracture trends in the Medicare data. The results from that study did not suggest that the ICD-10 version systematically identified a higher or lower number of fractures than the ICD-9 codes.

The evaluation period for nonvertebral fracture events will start from the index date (date of initial prescription dispensed) to the earliest of the following events:

a) First non-vertebral fracture event date (hip, pelvis, shoulder, radius or ulna, wrist, femur, tibia or fibula, ankle)

b) 18 months after the index date

c) In-hospital death

The evaluation period for hip fracture events will start from the index date (date of initial prescription dispensed) to the earliest of the following events:

a) first hip fracture event date

b) 18 months after index date

c) In-hospital death

7.6.7.2. Evaluation of Cardiovascular Safety

Evaluation of cardiovascular safety outcomes will be carried out for patients who have 18 months of follow-up data from their index date while on treatment with ABL or TPTD. The following data variables will be extracted:

- End of treatment date which is the last prescription date + supply day
- Date of the first incidence of MI
- Date of the first incidence of stroke
- Date of the first incidence of heart failure
- Date of in-hospital cardiovascular death
- Date of all-cause in-hospital death

7.7. Data Management

For this study there will be no new primary data collected. The study will be conducted using real-world (secondary) data for analysis. [redacted] software will be used to connect to the Cloudera Hadoop (CDH) 7.1.4-1 database for data extraction. R software may be used for PS matching. Datasets and tables, figures, and listings (TFLs) will be created on a Citrix Windows platform using SAS V9.4 M6.

7.8. Statistical Methods and Analyses

The study will use a convenience sample of patients who meet the study selection criteria. Medical and pharmacy claims will be used to determine the presence of conditions. International Classification of Diseases Clinical Modification, 9th Revision (ICD-9-CM) and 10th Revision (ICD-10-CM) codes will be used to assess comorbidities. National Drug Code (NDC) codes will be used to identify the anabolic drug (ABL or TPTD) and to identify prior and concomitant medications. Additionally, the Current Procedural Terminology (CPT) and Healthcare Common Procedure Coding System (HCPCS) will be used to support the derivation.

Detailed code lists are included in Fracture Algorithm (Appendix 2), Cardiovascular Event Codes (Appendix 3), Diagnostic Codes for All Comorbidities (Appendix 4), and NDC Codes and HCPCS Codes for Medications (Appendix 5).

7.8.1. Power and Sample Size

7.8.1.1. Sample Size

All patients who meet the inclusion criteria and do not meet any of the exclusion criteria will be included in the analysis. After PS matching, it is estimated that approximately 16,000 patients will be included in the analyses, 8,000 patients in each cohort.

7.8.1.2. Power Calculation

- Abaloparatide versus teriparatide with a noninferiority margin of 30%
    - Assuming a nonvertebral fracture rate of 3.5% at the end of 18 months
    - 8,000 matched subjects in each group
    - 95% power for HR up to 1.3

7.8.2. Creation of Analytic Cohorts and Source Data Characteristics

A flow diagram will be provided to reflect the order of operations used to create the analytic cohort from the source database. Temporality of assessment windows will be provided relative to the cohort entry (index date) including additional data to denote exclusion/inclusion criteria and how the final sample was derived.

A table about the source of data (pharmacy claims, medical claims, enhanced hospital claims) will be provided. The table will include calendar time cohort entry (index date) and calendar time range of available data in the pre-index and post-index assessment windows.

7.8.3. Analysis Populations

Analysis population are all patients meeting the study inclusion/exclusion criteria and selected after propensity matching. The same matched population will used for both effectiveness and safety analysis.

The effectiveness evaluation will be conducted using an ITT analysis, meaning that the first fracture event during the 18 months (+ 30 days follow-up) after the index date will be summarized regardless of when treatment ended. Cardiovascular safety outcomes will be evaluated using an As-Treated (AT) analysis based on only events occurring during the treatment period which is from the index date to the last prescription anabolic drug obtained within the 18 months after the index date, regardless of the anabolic drug possession gap between any 2 prescription fills.

7.8.4. Baseline Descriptive Statistics

Summary statistics will be provided for all demographic and clinical characteristics (Section 7.6.1) for both before and after PS matching of patients to the 2 treatment cohorts (ABL and TPTD). (See Appendix 4 for the list of baseline comorbidities, prior medications, previous fractures, fall risk, and prior cardiovascular risks.) Numbers and percentages will be provided for dichotomous and polychotomous variables. Means, medians, standard deviations, will be provided for continuous variables.

7.8.5. Propensity Score Matching

In the absence of randomization, logistic regression-based PS matching will be used to create the analytic cohorts from all patients meeting the study inclusion/exclusion criteria. A greedy matching algorithm with no replacement will be adopted. The default caliper, the number of standard deviations of the distance measure within which to draw control unit, will be set at 0.20 (Austin et al, 2011). Additional sensitivity analyses using a tighter (0.15) or wider (0.3) caliper will be carried out. Cohorts will be prospectively specified to match on age, prior fracture history, osteoporosis-related hospitalization, and chronic comorbidities and concomitant medications during the pre-index period that are associated with an increased fall risk (see Appendix 1 for the full list of matching variables). The R software MatchIt package (https://cran.r-project.org/web/packages/MatchIt/MatchIt.pdf) will be used to find matched pairs. Pre-match and post-match will be evaluated using prespecified criteria for mean standard difference to ensure that PS matching was successful. After matching, the mean standard difference on each covariate between ABL and TPTD is expected to be < 0.10.

7.8.6. Effectiveness Analyses

In this study, the primary analyses of effectiveness will be noninferiority analyses for ABL versus TPTD on time to the first incidence of nonvertebral fractures with a margin of 30%. Noninferiority of ABL to TPTD will be concluded if the upper bound of 2-sided 95% CI of HR between ABL versus TPTD is < 1.3.

In a recently published historical control observational study evaluating the real-world effectiveness of osteoporosis therapies using Medicare claim data between 2008 and 2011, the fracture incidence rates for the 12-month pre-treatment period were compared with the 12-month on-treatment period (Yusuf et al, 2018). For patients treated with TPTD, the incidence rate ratio (IRR [95% CI]) was 0.36 (0.31 to 0.41) for any fracture and 0.34 (0.32 to 0.36) for hip fracture. Based on the EMA and FDA noninferiority margin guidelines (EMA, 2005; FDA, 2016), if the upper boundary of ABL versus TPTD is HR < 1.3, then ABL will preserve approximately 70% of the TPTD benefit, which is higher than the minimum required threshold of 50%.

Comparisons of the time to fracture between the PS-matched ABL and TPTD groups will be based on a Cox proportional hazards model. The hazard ratio (HR) and 95% confidence interval (CI) between the 2 treatment groups will be calculated. The Kaplan-Meier method will be used to estimate event rates. Log rank test will be calculated.

For the fracture outcomes, and the corresponding sensitivity and subgroup analyses, patients will be followed for up to 18 months or until their first fracture event (for the fracture site of interest under evaluation), whichever comes first. All analyses are based on index medication cohort.

The duration, in days, from the date of the first filled prescription for ABL or TPTD to the first incidence of nonvertebral fracture will be derived. If a patient does not experience any nonvertebral fractures during the 18 months of treatment + 30-day follow--up (for a total of 19 months), the patient will be censored at the day of in-hospital death or the 19 months.

For the fracture outcomes, an ITT analysis will be applied. Patients will be followed for up to 18 months + 30-day follow-up, or until their first fracture event (for the fracture site of interest under evaluation) or in-hospital death, whichever comes first. Duration, in days, from the index date to the last follow-up date will be calculated. For calculation purposes, 1 month is equivalent to 30 days. All analyses are based on the patient's index medication cohort.

A nonvertebral fracture is any fragility fracture at the hip, pelvis, femur, ankle, shoulder (including shoulder, humerus, clavicle), radius/ulna, wrist, or tibia/fibula. Derivation details are provided in Appendix 2.

The time to the first incidence of hip fracture and the other 7 individual fracture sites will be summarized using similar methods as those used for nonvertebral fracture.

The Kaplan-Meier curves will be generated to graphically display the fracture event or 18 months plus 30-day follow-up.

7.8.7. Safety Analyses

A Cox proportional hazards model will be used for the time to first cardiovascular event. HR and 95% CIs will be presented.

The ICD-10 diagnosis from the hospital claim and physician claim will be used to derive post-index myocardial infarction (MI) (I21.x, I22.x), stroke (I61.x – I63.x), or heart failure (I50.x, excluding I50.x2, I50.8x). Hospital discharge status code (20 to 29 or 40 to 42) will be derived for in-hospital death. A detailed code list is provided in Appendix 3. Subjects with in-hospital cardiovascular death derived from indirect approach 2 (Xie et al, 2018) will be included in the analyses. 2018 ICD-10 CM and General Equivalence Mappings (GEMS) from the Centers for Medicare & Medicaid (CMS) (will be used to translating ICD-9 CM to ICD-10 CM (CMS, 2018).

The As-Treated (AT) analysis will be conducted for the safety evaluation. The first incidence of a cardiovascular event after the index date and before the 30 days after the end of treatment will be analyzed.

A cardiovascular event is the first incidence of the composite endpoint of nonfatal MI, nonfatal stroke, or in-hospital cardiovascular death; the first incidence of the composite incidence of nonfatal MI, nonfatal stroke, heart failure or in-hospital cardiovascular death; or the first incidence of MI, stroke, heart failure, or in-hospital cardiovascular death separately.

7.8.8. Anabolic Drug Exposure

The overall duration of cohort anabolic drug exposure will be summarized for PS-matched patients.

> Overall Duration of Anabolic Drug Exposure (day) = Date of last anabolic drug prescription fill + Supply days – index date + 1

Consecutive treatment duration is determined from the index date to the last drug supply date without any gap exceeding 60 days.

Because the efficacy and safety evaluations are limited to an 18-month period, the overall duration of the anabolic drug exposure will be cut off at 540 days, even if the patient used the anabolic drug (ABL or TPTD) for > 18 months.

7.8.9. Concomitant Use of Osteoporosis Treatment

Between the index date and the end of the Treatment Period (18 months + 30-day follow-up period), use of any osteoporosis treatment options other than ABL or TPTD will be summarized for the PS-matched populations.

7.8.10. Sensitivity Analyses

7.8.10.1. Population Selection

To evaluate the stability of the PS matched cohorts, 2 different calipers (0.15, 0.3) will be carried out to the PS matching. The sensitivity analyses on effectiveness and safety endpoints will be performed on these matching populations.

Sensitivity analyses on effectiveness and safety endpoints will be performed on sub population with each of additional exclusion criteria:

- Exclude patients without a minimum of 12 months of anabolic drug exposure:
  (1) 12-consecutive months of anabolic drug exposure as assessed by medication dispensed; and
  (2) 12-month cumulative anabolic drug exposure during the 18-month follow-up
- Exclude patients with prescriptions dispensed for ≤ 1 month, 3 months, 6 months, and 9 months
- Exclude patients with previous use of denosumab or zoledronic acid

7.8.10.2. Safety Endpoints

All-cause in-hospital death without any restriction will replace in-hospital cardiovascular death as the sensitivity analysis on secondary safety endpoints.

The cardiovascular events (MI, stroke, and heart failure) in the secondary endpoint is the first post-index incidence recorded on a hospital claim or physician claim. To evaluate possible overestimation, new incident of MI, stroke, or heart failure as no previous diagnosis in the 183 days preceding the index date as in the Sentinel Initiative (Cutrona et al, 2013) will be carried as a sensitivity analysis.

7.8.11. Subgroup Analyses

The absence of BMD data is a limitation of the study because BMD is often used for risk assessment. Instead, we propose to evaluate patients based on previous fracture history, which is the greatest predictor of future fracture risk (Banefelt et al, 2019; Balasubramanian et al, 2019).

We propose to have a subgroup analysis of patients with previous bisphosphonate use. Most (64.7%) of patients in the EU had previously used bisphosphonates (Langdahl et al, 2018). Additional subgroup analyses include evaluation of outcomes by age group and by race/ethnicity.

7.8.11.1. Subgroup Analyses for Effectiveness:

The following subgroup analyses will be performed:

- Age group: < 75 years vs. ≥ 75 years
- Race/ethnicity: White, Hispanic, African American, Asian, Other, Unknown, Missing
- Prior use of bisphosphonates within 5 years before the index date: with vs. without
- Prior fracture within 1 year before the index date: with vs. without

Each subgroup will be PS-matched separately to ensure the comparability between the patients in the ABL and TPTD groups.

7.8.11.2. Subgroup Analyses for Safety:

Subgroup analyses will be performed by:

- Age group (age < 75 years vs. age ≥ 75 years)
- Race/ethnicity: White, Hispanic, African American, Asian, Other, Unknown, Missing
- With or without prior cardiovascular risk
- With or without MI or stroke within 1 year before the index date.

Each subgroup will be PS-matched separately to ensure the comparability between ABL and TPTD.

7.9. Quality Assurance

Outlined by phase below is PRA Medical Informatics' Codes Review and Quality Control procedure:

1.	**Pre-Programming Quality Control**	In this phase, the Internal Developer will ensure access to all data tables is available, as well as ensure all clinical codes given by the Clinical Lead are aligned with PRA internal standard reference data management tables in the database.
2.	**Code Quality Control Documentation**	In this phase, the Internal Developer will ensure the QC documentation captures each step of the coding process and details all requirements each step is required to implement, the database tables used and/or created as well as the desired outcomes.
3.	**Code Quality Control Review**	In this phase, the Internal Developer and the Peer QC Analyst will walk through the entirety of the code section by section ensuring the code matches the Technical Specifications Document and is producing the desired outcomes. A Quality Gate Acceptance/Failure designation will be assigned at each step in the QC documentation. If a Quality Gate fails at a specific point, the root cause of the failure will be determined (ie, coding errors, problematic business rules, etc.) and appropriate corrective action will be taken. If there has been a coding error, the Internal Developer will correct the error, re-run the code, and produce the requisite outputs. If one or more business rules are causing problems, the business rules may need to be modified. Any business rule modifications will need Project Manager sign-off and be detailed on any documentation going back to the client.

Regardless of the failure, the Quality Control phases will be repeated to ensure the issues have be corrected. (if so, modifications to the business rules may be necessary to match the produced results), or data (if so, additional steps may be required to clean the data as needed to achieve the expected results).

8. PROTECTION OF HUMAN SUBJECTS

The terms of the Research Exception provisions of the Privacy Rule, 45 CFR 164.514(e) exempt Institutional Review Board approval for this non-experimental study, which is fully HIPAA compliant. Data are maintained in a de-identified manner, thus are not subject to institutional review board.

No patients will be directly contacted for participation in the study and no intervention will be provided as part of the protocol. The study will use a secondary data source containing de-identified data.

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The design of this study is characterized by secondary use of data previously collected from health insurance claims. Thus, for this study the submission of suspected adverse reactions in the form of Individual Case Safety Reports (ICSRs) is not required. The study design was retrospective and there were no claims adjudication. No validated algorithm was used to confirm events were incident events. Claims are therefore only "proxies" for events.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study will be registered on ClinicalTrials.gov. The results from this retrospective cohort study evaluating real-world evidence will be submitted as a manuscript to a peer-reviewed journal.

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12. APPENDICES

Appendix 1: List of Parameters for Propensity Score Matching

Appendix 2: Fracture Algorithm

A claims-based algorithm with high specificity for fracture site will be used for evaluation of treatment effectiveness (Wright et al, 2019).

1. All claims with a fracture diagnosis in any position will be evaluated starting 5 years before index to 19 months (18 months plus 30 days follow up, 1 month = 30 days) after index date.

2. Case-qualifying (CQ) fractures are those identified during an inpatient stay or in an outpatient setting accompanied by a fracture repair procedure code on the same day.

3. CQ fracture diagnoses and non-CQ fracture diagnoses will then be used to extend the fracture episode for evaluation of subsequent fractures. Episodes at the same site continued until a gap of 90 days is observed between consecutive claims.

Fracture diagnoses will be based on primary or secondary ICD-9 code before October 2015 or ICD-10 code after that date listed on the same claim.

Appendix 3: Cardiovascular Event Codes

Appendix 4: Diagnostic Codes for All Comorbidities

Appendix 5: National Drug Code (NDC) Codes and HCPCS Codes for the Medications Used