Summary Table of Study Protocol

Title	*Integrated Retrospective Analysis of Metastatic-related and Non-metastatic-related Fractures in Studies 20050136, 20050244, and 20050103.*
Protocol version identifier	*20180024*
Date of last version of the protocol	*29 January 2018*
EU Post Authorisation Study (PAS) Register No	*NA*
Active Substance	Denosumab
Medicinal Product	XGEVA®
Product Reference	AMG162
Procedure Number	N/A
Joint PASS	*Yes*
Research Question and Objectives	Descriptive analysis of on-study metastatic and non-metastatic fractures from studies 20050136, 20050103,and 20050244 in subjects with bone metastases from solid tumors To describe additional risk factors associated with on-study non-metastatic fractures for subjects with on-study non-metastatic fracture(s) This study will fulfil a postmarketing commitment to the US Food and Drug Administration (FDA) (part of the approval of XGEVA® prior approval supplement which added Multiple Vertebral Fractures (MVF) Following Treatment Discontinuation to Warnings & Precautions section of XGEVA US Prescribing Information).
Country(-ies) of Study	N/A
Author	PPD Clinical Research Medical Director, Amgen Inc Tel: PPD PPD Biostatistics Senior Manager, Amgen Inc

Marketing Authorization Holder

Marketing authorization holder(s)	Amgen Inc
MAH Contact	PPD

Confidentiality Notice

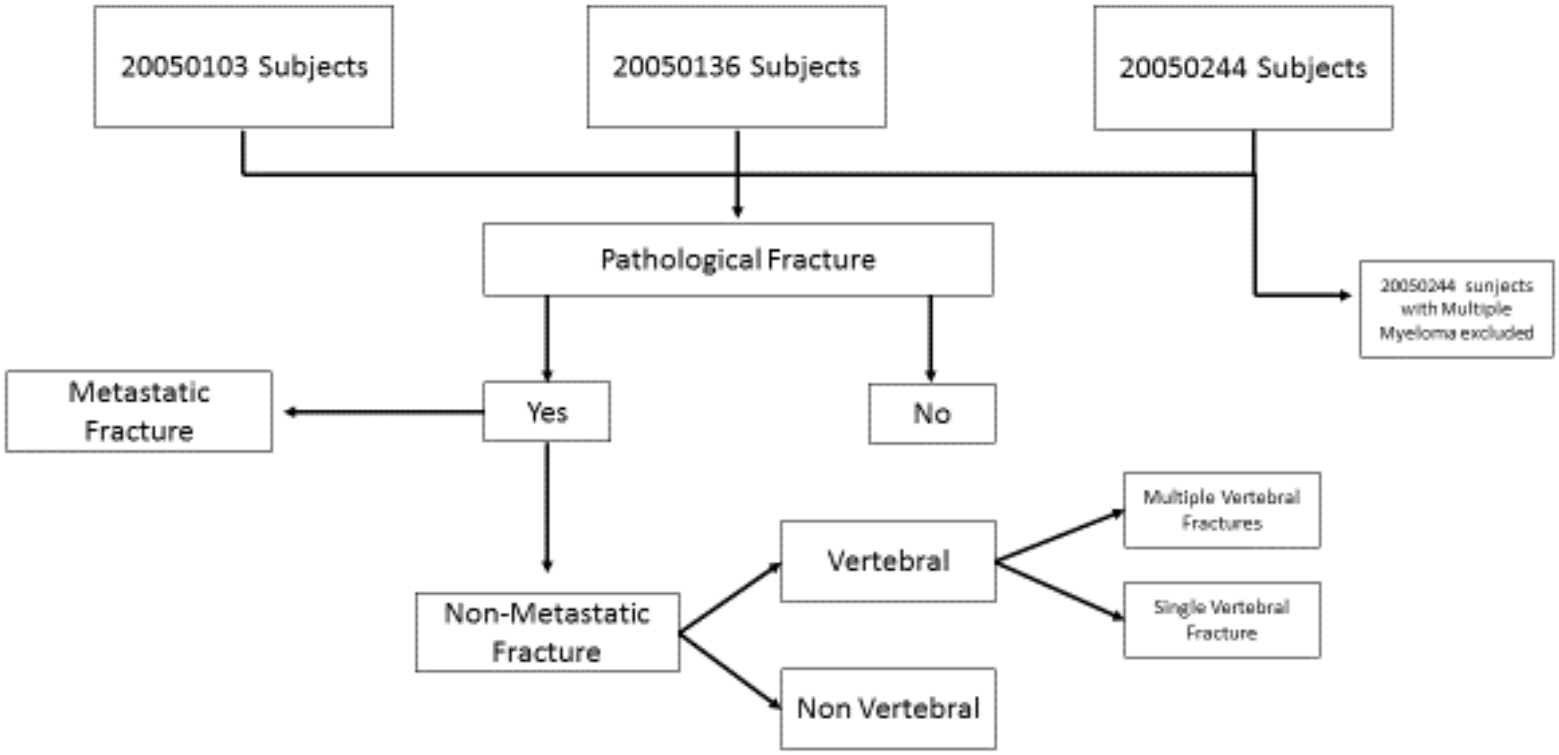
This document contains confidential information of Amgen Inc.

This document must not be disclosed to anyone other than the site study staff and members of the Institutional Review Board/Independent Ethics Committee/Institutional Scientific Review Board or equivalent, as applicable.

The information in this document cannot be used for any purpose other than the evaluation or conduct of the research without the prior written consent of Amgen Inc.

If you have questions regarding how this document may be used or shared, call the Amgen Medical Information number: *1-800-77-AMGEN,*

Figure 1. Study Design



1. Table of Contents

List of Tables

List of Figures

List of Appendices

2. List of Abbreviations

Abbreviation or Term	Definition/Explanation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMD	bone mineral density
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
IV	intravenously
MRI	magnetic resonance imaging
PMC	post-marketing commitment
Q4W	every 4 weeks
RANKL	RANK ligand
SDTM	Study Data Tabulation Model
SRE	skeletal-related event (defined as pathologic fracture [vertebral or non-vertebral], radiation therapy to bone [including use of radioisotopes], surgery to bone, or spinal cord compression)
TNF	tumor necrosis factor
TRAIL	TNF-related apoptosis inducing ligand
ULN	upper limit of normal
US	United States

3. Responsible Parties

Key Sponsor Contact

PPD

Clinical Research Medical Director
Amgen Inc, 1 Amgen Center Drive, Thousand Oaks, CA 91320
Tel: PPD

Internal Collaborators

PPD

Biostatistics Senior Manager, Amgen Inc

External Collaborators

Professor PPD, MBBS, MD, FRCP, FRCPE

Emeritus Professor of Medical Oncology, Department of Oncology & Metabolism,
University of Sheffield, Weston Park Hospital, Sheffield, S10 2SJ

4. Abstract

Integrated Retrospective Analysis of Metastatic-related and Non-metastatic-related Fractures in Studies 20050136, 20050244, and 20050103

Study Background and Rationale

Bone metastases occur in more than 1.5 million patients with cancer worldwide (Coleman et al, 2005b) and are most commonly implicated in cancers of the prostate, lung, and breast, with incidence rates as high as 75% (Selvaggi et al, 2005; Carlin et al, 2000; Coleman, 1997; Viadana et al, 1973). Bone metastases can result in incapacitating clinical sequelae (Coleman et al, 2006). These complications include debilitating pain that often requires aggressive management with radiation therapy and narcotic analgesics, pathologic fractures that may impair ambulation, surgery to prevent or treat pathologic fractures or manage pain, and spinal cord compressions that can result in numbness or weakness, urinary or fecal incontinence, and paralysis. Furthermore, skeletal complications of bone metastases have been associated with increased mortality (Lage et al, 2008; DePuy et al, 2007).

Denosumab is a fully human monoclonal IgG2 antibody to RANK ligand (RANKL) that binds with high affinity (Kd 3 x 10-12 M) and specificity to the soluble and cell membrane-bound forms of human RANKL. Denosumab is highly specific because it binds only to RANKL and not to other members of the tumor necrosis factor (TNF) family, including TNFα, TNFβ, TNF-related apoptosis inducing ligand (TRAIL), or CD40 ligand (Elliott et al, 2006; Kostenuik et al, 2009). Denosumab binding prevents the activation of RANK and inhibits the formation, activation, and survival of osteoclasts [Buijs et al, 2009; Clezardin et al, 2007; Boyle et al, 2003]). As a consequence, bone resorption and cancer-induced bone destruction are reduced.

In over 70 countries, denosumab has an approved indication in patients with cancer as follows: XGEVA is indicated for the prevention of skeletal-related events (SREs) in patients with bone metastases from solid tumors. The development program leading to marketing authorization included 3 phase 3 studies comparing the clinical benefit of denosumab with another bone-modifying agent, zoledronic acid. The studies used the endpoint of skeletal related events (SREs), which were defined in these studies as pathologic fracture (excluding major trauma), radiation therapy to bone, surgery to bone, or spinal cord compression. The benefit of denosumab 120 mg for prevention of SREs in patients with solid tumors has been demonstrated in a large clinical study program. Subjects with advanced breast cancer, solid tumor or multiple myeloma, and metastatic

castrate-resistant prostate cancer were recruited (US Prescribing Information for XGEVA [denosumab]); denosumab delayed the time to first SRE following randomization as compared with zoledronic acid in subjects with breast or castrate-resistant prostate cancer (CRPC) with osseous metastases. In subjects with bone metastasis due to other solid tumors or lytic lesions due to multiple myeloma, denosumab was noninferior to zoledronic acid in delaying the time to first SRE following randomization.

The safety profile of denosumab has been extensively characterized in the clinical development program, and has been enhanced by postmarketing safety surveillance. Furthermore the adverse effect profile of the bisphosphonates, approved in some markets for cancer metastases indications, are associated with some similar risks such as hypocalcemia, osteonecrosis of the jaws, and atypical femur fracture in addition to adverse renal toxicity and acute phase responses which have not been observed with denosumab. Based on ongoing evaluation of denosumab in clinical studies and the postmarketing setting, the benefit:risk profile of XGEVA (denosumab 120 mg every 4 weeks [Q4W]) in the prevention of SREs in patients with advanced cancers is favorable. XGEVA offers a meaningful advance in treatment for the prevention of SREs in patients with bone metastases from solid tumors.

In January 2018, a safety update was approved by the US FDA to add Multiple Vertebral Fractures (MVF) Following Treatment Discontinuation to the warnings and precautions section of the XGEVA USPI. Since the FDA were unable to observe the phenomenon of MVF in the solid tumor patient setting following treatment discontinuation, the Agency would like to ensure that the safety and efficacy is maintained during the active treatment period. Therefore, the FDA want to explore whether or not XGEVA is detrimental to bone for non-pathological fractures. As part of the approval, Amgen agreed to the following post-marketing commitment (PMC): “Perform a retrospective analysis in Metastatic-related and Non-metastatic-related Fractures in clinical trials 20050136, 20050244 and 20050103, leading to XGEVA approval in patients with bone metastases from solid tumors, during the active treatment period, and characterize the non-metastatic fractures. Submit the final report with labeling.” This proposed study is designed to address these objectives and will fulfil the PMC.

Research Question and Objective(s)

- **Primary Objective(s)**

  To characterize the on-study metastatic and non-metastatic fractures seen in studies 20050136, 20050244 and 20050103. A metastatic fracture is a fracture diagnosed at a site where a bone metastases is present. Non-metastatic fractures are all other fractures diagnosed. Location of non-metastatic fracture (vertebral vs non-vertebral) and Fracture Common Terminology Criteria for Adverse Events (CTCAE) grades will be assessed.

  - G1: Asymptomatic, radiographic findings only (eg, asymptomatic rib fracture on plain x-ray, pelvic insufficiency fracture on magnetic resonance imaging [MRI], etc.)
  - G2: Symptomatic but non- displaced; immobilization indicated
  - G3: Symptomatic and displaced or open wound with bone exposure; operative intervention indicated
  - G4: Disabling; amputation indicated
  - G5: Death

- **Secondary Objective(s)**

  To describe baseline medications known to decrease bone mineral density (BMD) and/or a history of osteoporosis in those patients experiencing a non-metastatic fracture.

- **Hypothesis(es)/Estimation**

  No hypothesis testing will be conducted for this study

Study Design/Type

This study is a retrospective, Amgen database analysis of subjects with bone metastases from solid tumors in studies 20050136, 20050244 and 20050103.

Study Population or Data Resource

Subjects with bone metastases from solid tumors who experienced an on-study fracture in studies 20050136, 20050244 and 20050103.

Summary of Eligibility Criteria

All subjects randomized on Studies 20050136, 20050103, and 20050244 (excluding 179 subjects with multiple myeloma) will be included in the analysis. Eligibility criteria for this study are the same as the eligibility criteria used for enrollment in the original studies

Variables

- Outcome Variable(s)
  Subjects with an on-study fracture will be identified. Using location codes from the imaging charter, fractures will be defined as metastatic or non-metastatic, then vertebral or non-vertebral for non-metastatic. Fracture Common Terminology Criteria for Adverse Events (CTCAE) grades will be recorded.
- Exposure Variable(s)
  Number of doses received for subjects with fractures

Study Sample Size

The integrated database for studies 20050103, 20050136, and 20050244 includes 5723 randomized subjects. Excluding the subjects with multiple myeloma (n=179), a total of 5544 subjects (denosumab n = 2776; zoledronic acid n = 2768) will be included in the analysis.

Data Analysis

The event rates of metastatic and non-metastatic fractures will be calculated based on the total number of fractures. The crude rate and its 95% confidence intervals will be calculated for the denosumab and zoledronic acid groups for the pooled data as well as for each individual study.

For non-metastatic fractures, location of fracture (vertebral vs non-vertebral) and fracture CTCAE grade will be summarized.

The subject incidence of fracture will be calculated based on all randomized subjects with solid tumors.

The baseline medications known to affect bone density and or history of osteoporosis will be summarized descriptively for subjects with at least 1 non-metastatic fracture.

Subjects will be analyzed according to their original treatment assignment, regardless of treatment received.

5. Amendments and Updates

None

6. Milestones

Milestone	Planned Timeline
Start of data collection	*December 2018*
End of data collection	*March 2019*
Final report of study results	*June 2019*

7. Rationale and Background

7.1 Diseases and Therapeutic Area

Bone metastases occur in more than 1.5 million patients with cancer worldwide (Coleman et al, 2005b) and are most commonly implicated in cancers of the prostate, lung, and breast, with incidence rates as high as 75% (Selvaggi et al, 2005; Carlin et al, 2000; Coleman et al, 1997; Viadana et al, 1973). Bone metastases can result in incapacitating clinical sequelae (Coleman et al, 2006). These complications include debilitating pain that often requires aggressive management with radiation therapy and narcotic analgesics, pathologic fractures that may impair ambulation, surgery to prevent or treat pathologic fractures or manage pain, and spinal cord compressions that can result in numbness or weakness, urinary or fecal incontinence, and paralysis. Furthermore, skeletal complications of bone metastases have been associated with increased mortality (Lage et al, 2008; DePuy et al, 2007).

The underlying pathophysiology of bone metastases, irrespective of primary tumor type and their radiographic appearance, is a locally increased pathologic rate of bone remodeling, including increased osteoclast activity (Roodman, 2004; Yonou et al, 2004). Increased osteoclast activity can be demonstrated by histology (Roudier, 2008) and by elevated levels of serum bone resorption markers (Demers et al, 2003). Elevated levels of bone resorption, as measured by increases in bone resorption markers, have been associated with worse prognosis for significant skeletal morbidity (Coleman et al, 2005a). As above, the clinical consequences of increased osteoclastic activity associated with pathological bone remodeling in the setting of bone metastases may lead to fracture, radiation therapy, or surgery to bone to alleviate bone pain and/or prevent impending fracture, spinal cord or nerve compression, and hypercalcemia of malignancy. As a composite, the local irreversible events (fractures, radiation to bone, spinal cord compression, or surgery to bone) are defined as skeletal related events (SREs), whereas hypercalcemia of malignancy is a systemic and potentially reversible event and is not considered to be a component of SREs by the regulatory authorities.

A key objective in managing the skeletal morbidity associated with bone metastases is to inhibit excessive osteolysis and interrupt the vicious cycle of bone destruction, tumor growth, and further bone destruction, thus preventing or delaying the complications from bone metastases. The pharmacologic armamentarium in the United States for this indication currently comprises intravenous (IV) bisphosphonates (eg, zoledronic acid, pamidronate), which have been shown to reduce the incidence of SREs in patients with advanced cancer and bone metastases (Kohno et al, 2005; Saad et al, 2002; Rosen et al, 2003; Rosen et al, 2001; Theriault et al, 1999; Berenson et al, 1996; Hortobagyi et al, 1996) and act by reducing bone resorption through inhibition of mature osteoclast activity (Zometa et al, 2011). Suppression of bone resorption and formation markers has been observed following bisphosphonate treatment (Body et al, 2003). These data, as well as data from nonclinical models (Roodman et al, 2008), suggest that inhibition of osteoclast activity leads to a reduction in cancer-induced bone destruction and support the use of antiresorptives as treatment for bone metastases. Currently, in addition to systemic antitumor therapy, treatment with IV bisphosphonates (eg, zoledronic acid, pamidronate) is recommended for patients with bone metastases (Carlson et al, 2011; Theriault et al, 2006; Warr et al, 2004; Hillner et al, 2003). Of the currently available IV bisphosphonates, zoledronic acid is considered the standard of care, with demonstrated efficacy across tumor types (Kohno et al, 2005; Saad et al, 2002; Rosen et al, 2004; Rosen et al, 2001) and greater potency compared to other bisphosphonates (Gutta et al, 2007).

Despite the availability of bisphosphonate treatment, an opportunity exists to improve the management of skeletal complications in patients with bone metastases (Clark et al, 2008; Coleman et al, 2008). A substantial proportion of patients (between approximately 30% to 50%) continue to experience these complications (Rosen et al, 2004; Rosen et al, 2001; Saad et al, 2002), indicating that additional treatment options are warranted. In addition, bisphosphonates are not recommended for use in patients with severe renal impairment because this therapy has been associated with an increased risk of clinically significant deterioration in renal function (Zometa et al, 2011; Aredia et al, 2011). Renal deterioration is a prevalent condition in patients with advanced cancer, with decreased renal function observed in approximately 50% to 60% of patients with solid tumors, including breast cancer (Launey-Vacher et al, 2010; Kleber et al, 2007). Therefore, minimizing exposure to drugs that may increase the risk of nephrotoxicity, such as bisphosphonates, is an important consideration in the treatment of these patients. Denosumab, by virtue of its anti-osteoclastic properties, would be expected to

be effective in reducing the occurrence of SREs in patients with bone lesions from solid tumors or multiple myeloma.

Denosumab is a fully human monoclonal IgG2 antibody to RANK ligand (RANKL) that binds with high affinity (K_d = 3 x 10^{-12} M) and specificity to the soluble and cell membrane-bound forms of human RANKL. Denosumab is highly specific because it binds only to RANKL and not to other members of the tumor necrosis factor (TNF) family, including TNFα, TNFβ, TNF-related apoptosis inducing ligand (TRAIL), or CD40 ligand (Elliott et al, 2006; Kostenuik et al, 2009). Denosumab binding prevents the activation of RANK and inhibits the formation, activation, and survival of osteoclasts [Buijs et al, 2009; Clezardin et al, 2007; Boyle et al, 2003]). As a consequence, bone resorption and cancer-induced bone destruction are reduced.

In over 70 countries, denosumab has an approved indication in patients with cancer as follows: XGEVA is indicated for the prevention of SREs in patients with bone metastases from solid tumors. The development program leading to marketing authorization included, 3 phase 3 studies were conducted comparing the clinical benefit of denosumab with another bone-modifying agent, zoledronic acid. The studies used the endpoint of SREs, which were defined in these studies as pathologic fracture (excluding major trauma), radiation therapy to bone, surgery to bone, or spinal cord compression. The benefit of denosumab 120 mg for prevention of SREs in patients with solid tumors has been demonstrated in a large clinical study program. Subjects with advanced breast cancer, solid tumor or multiple myeloma and metastatic castrate-resistant prostate cancer were recruited (US Prescribing Information for XGEVA [denosumab]); denosumab delayed the time to first SRE following randomization as compared with zoledronic acid in subjects with breast or castrate-resistant prostate cancer (CRPC) with osseous metastases. In subjects with bone metastasis due to other solid tumors or lytic lesions due to multiple myeloma, denosumab was noninferior to zoledronic acid in delaying the time to first SRE following randomization.

7.2 Rationale

In January 2018, a safety update was approved by the US FDA to add Multiple Vertebral Fractures (MVF) Following Treatment Discontinuation in to the warnings and precautions section of the XGEVA USPI. Since the FDA were unable to observe the phenomenon of MVF in the solid tumor patient setting following treatment discontinuation, the Agency would like to ensure that the safety and efficacy is maintained during the active treatment period. Therefore, the FDA want to explore whether or not XGEVA is

detrimental to bone for non-pathological fractures. As part of the approval, Amgen agreed to the following postmarketing commitment: "Perform a retrospective analysis in Metastatic-related and Non-metastatic-related Fractures in clinical trials 20050136, 20050244 and 20050103, leading to XGEVA approval in patients with bone metastases from solid tumors, during the active treatment period, and characterize the non-metastatic fractures. Submit the final report with labeling. This proposed study is designed to address these objectives and will fulfil the PMC.

7.3 Statistical Inference (Estimation or Hypothesis[es])

There is no formal hypothesis to be tested. The event rates of metastatic and non-metastatic fracture will be estimated.

8. Research Question and Objectives

8.1 Primary

The primary objective is to characterize the on-study metastatic and non-metastatic fractures seen in the 20050136, 20050244 and 20050103 studies. Location of non-metastatic fracture (vertebral vs non-vertebral) and fracture CTCAE grades will be assessed.

- G1: Asymptomatic, radiographic findings only (eg, asymptomatic rib fracture on plain x-ray, pelvic insufficiency fracture on MRI, etc.)
- G2: Symptomatic but non- displaced; immobilization indicated
- G3: Symptomatic and displaced or open wound with bone exposure; operative intervention indicated
- G4: Disabling; amputation indicated
- G5: Death

8.2 Secondary

The secondary objective is to describe baseline medications known to reduce bone mineral density (BMD) and/or a history of osteoporosis in those patients experiencing a non-metastatic fracture.

9. Research Methods

9.1 Study Design

This study is a retrospective, Amgen database analysis of subjects in the 20050136, 20050244, and 20050103 studies in subjects with bone metastases from solid tumors.

9.2 Setting and Study Population

The population of studies 20050136, 20050244, and 20050103 is subjects with bone metastases from solid tumors. These were double-blinded studies with subjects

receiving either denosumab 120 mg Q4W or zoledronic acid 4 mg Q4W. The cohort of subjects with multiple myeloma from Study 20050244 will be removed for the purposes of this analysis following the FDA request to analyze subjects with solid tumors only.

9.2.1 Study Period

20050103 Blinded Treatment Analysis	
First subject enrollment date:	12 May 2006
Last subject enrollment date	18 December 2008
Blinded treatment analysis data cutoff date:	26 February 2010
20050136 Blinded Treatment Analysis	
First subject enrollment date:	17 April 2006
Last subject enrollment date	31 December 2007
Primary analysis data cutoff date:	6 March 2009
Blinded treatment analysis data cutoff date:	20 July 2009
20050244 Blinded Treatment Analysis	
First subject enrollment date:	21 June 2006
Last subject enrollment date	16 May 2008
Blinded treatment analysis data cutoff date:	30 April 2009
Last subject end of study date:	21 October 2009

9.2.2 Subject/Patient/Healthcare Professional Eligibility

9.2.2.1 Inclusion Criteria

All subjects randomized on Studies 20050136, 20050103, and 20050244 (excluding 179 subjects with multiple myeloma) will be included in the analysis. Eligibility criteria for this study are the same as the eligibility criteria used for enrollment in the original studies

Subject consent was previously obtained in the original studies. For the purposes of this analysis, no additional subject consent is required.

9.2.2.2 Exclusion Criteria

Subjects in the 20050244 study with multiple myeloma

9.2.3 Matching

Not Applicable

9.2.4 Baseline Period

Baseline value is the closest recorded measurement on or before the time of the first dose of either denosumab or zoledronic acid, the investigational product (IP). If a subject did not receive IP, baseline is the latest recorded measurement on or before the enrollment date.

Note: If the pre-dosing skeletal survey is not available, the first available post-dosing skeletal survey will be considered baseline by the central imaging vendor and indicated in the database.

9.2.5 Study Follow-up

Subjects in the 20050136, 20050244, and 20050103 studies were followed from the first dose of blinded investigational product until the end of the blinded study treatment phase.

9.3 Variables

9.3.1 Exposure Assessment

- the total dose of investigational product
- the number of days on study

9.3.2 Outcome Assessment

- Event rates of metastatic and non-metastatic fractures: The event rates of metastatic and non-metastatic fractures will be calculated based on all fractures.
- Event rates of vertebral and non-vertebral fractures: The event rates of vertebral and non-vertebral fractures will be calculated based on all non-metastatic fractures.
- Vertebral fractures per severity grade: The proportion of each severity grade will be calculated based on all vertebral fractures.
- Subject incidence of fracture: Subject incidence of fracture will be calculated based on all randomized subjects with solid tumors.
- In those subjects with a non-metastatic fracture, the proportion of those subjects taking medication known to reduce BMD and/or a history of osteoporosis.
- All above outcome assessments will be analyzed for subjects receiving zoledronic acid versus denosumab.

9.3.3 Validity and Reliability

The double-blind extension data set consists of subject-level data that has been checked and verified as accurate by Amgen. These data have already been reviewed and approved by regulators as a basis for the current approved indication of prevention of SREs in the XGEVA USPI. An imaging charter was designed with the third-party imaging vendor to ensure consistent documentation of bone metastasis locations and fracture diagnosis and locations. An analysis limitation exists, as described elsewhere in

this protocol, that the location coding of fracture sites is more general than that of bone metastases sites. Therefore, a weakness in the proposed analysis exists for identifying non-metastatic fractures (Section 9.8)

9.4 Data Sources

The data sources include the subject-level data for fracture and metastasis provided by RadPharm, a central imaging vendor. An integrated database for studies 20050103, 20050136, and 20050244 will be generated using raw/Study Data Tabulation Model (SDTM) data.

The Bone Site Code Descriptors list will be used on the RadPharm Source Document and is listed below in Table 1.

Table 1. Musculoskeletal Site Codes

Fracture Codes

Site Code	Fracture Site	Site Code	Fracture Site	Site Code	Fracture Site
F01	Skull	F09	Ribs	F27	Fibula
F02	Facial	F10	Sternum	F28	Tibia
F03	Mandible	F13	Clavicle	F32	Ilium
F04	Cervical vertebrae	F14	Scapula	F33	Ischium
F05	Thoracic vertebrae	F15	Humerus	F34	Pubis
F06	Lumbar vertebrae	F16	Radius	F50	Femur
F07	Sacrum	F17	Ulna	F88	Other (specify)
F08	Coccyx	F26	Patella		

Bone Metastasis Code

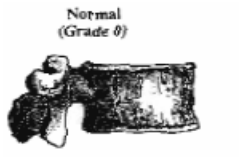
Site Code	Bone	Site Code	Bone	Site Code	Bone	Site Code	Bone
351	C1	R350	Right Skull	400	Sacrum	R335	Right Wrist
352	C2	L350	Left Skull	R401	1st Right Rib	L335	Left Wrist
353	C3	R380	Right Humerus	R402	2nd Right Rib	R336	Right Elbow
354	C4	L380	Left Humerus	R403	3rd Right Rib	L336	Left Elbow
355	C5	R381	Right Radius	R404	4th Right Rib	R337	Right Shoulder
356	C6	L381	Left Radius	R405	5th Right Rib	L337	Left Shoulder
357	C7	R382	Right Ulna	R406	6th Right Rib	R338	Right Hip
358	T1	L382	Left Ulna	R407	7th Right Rib	L338	Left Hip
359	T2	R383	Right Hand	R408	8th Right Rib	R339	Right Knee
360	T3	L383	Left Hand	R409	9th Right Rib	L339	Left Knee
361	T4	R384	Right Ribs	R410	10th Right Rib	R340	Right Ankle
362	T5	L384	Left Ribs	R411	11th Right Rib	L340	Left Ankle
363	T6	R385	Right Pelvis	R412	12th Right Rib	R341	Right Sacroiliac
364	T7	L385	Left Pelvis	L401	1st Left Rib	L341	Left Sacroiliac
365	T8	R386	Right Femur	L402	2nd Left Rib	R342	Right Acromioclavicular
366	T9	L386	Left Femur	L403	3rd Left Rib	L342	Left Acromioclavicular
367	T10	R387	Right Tibia	L404	4th Left Rib	R343	Right Sternoclavicular
368	T11	L387	Left Tibia	L405	5th Left Rib	L343	Left Sternoclavicular
369	T12	R388	Right Fubula	L406	6th Left Rib	R344	Other
370	L1	L388	Left Fibula	L407	7th Left Rib	L344	Other
371	L2	R389	Right Ankle	L408	8th Left Rib		
372	L3	L389	Left Ankle	L409	9th Left Rib		
373	L4	R390	Right Foot	L410	10th Left Rib		
374	L5	L390	Left Foot	L411	11th Left Rib		
375	S1			L412	12th Left Rib		
376	S2						
377	S3						
378	S4						
379	S5						

Evaluation of Vertebral Fracture

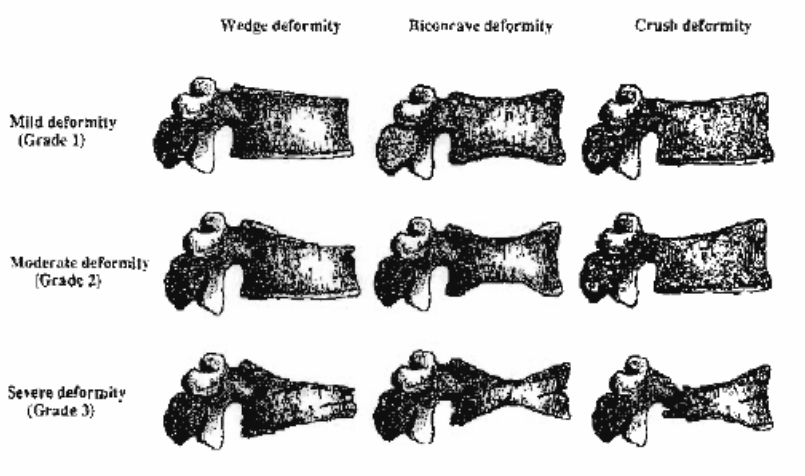
In studies 20050136, 20050103, and 20050244, each subject underwent skeletal survey every 12 weeks that the subject was on study. In addition, subjects could have undergone unscheduled skeletal assessments. Therefore, the time points evaluated are baseline, then every 12 weeks until end of study or withdrawal of consent, and unscheduled assessments

Vertebral fractures from the first cervical level (C1) to the fifth sacral level (S5) will be graded using the semi-quantitative grading scale of Genant (Genant et al, 1993) modified as follows: ·

No (no vertebral fracture present): Grade 0, normal



Yes (vertebral fracture present): Grade 1, > 20% reduction in vertebral height (anterior, middle, or posterior)



Each vertebra from C1 to S5 will be assigned a grade (Grade 0, Normal or Grade 1, Abnormal) at each time point as described above. Vertebral bodies will be numbered in the 400 series (400, 401, etc.) for this evaluation.

Evaluation of Non-vertebral Fracture

In the event the subject had any non-vertebral fracture while on study, the investigator should send the images diagnosing the fracture to RadPharm. The RadPharm reviewers will review the images and determine if a fracture is present. If present, the fracture will be recorded and annotated using the circle tool on the reading application.

The site codes, descriptors, and exam number will be recorded for each. New non-vertebral fractures will be numbered in the 500 series (500, 501, etc.) for this evaluation.

Information regarding trauma, as collected at the investigational site, will not be provided to RadPharm. Therefore, any fracture seen radiographically by RadPharm will be identified and reported as an SRE.

9.5 Study Size

The integrated database for Studies 20050103, 20050136, and 20050244 includes 5723 randomized subjects. Excluding the subjects with multiple myeloma (n=179), a total of 5544 subjects (denosumab n = 2776; zoledronic acid n = 2768) will be included in the analysis.

9.6 Data Analysis

9.6.1 Planned Analyses

9.6.1.1 Primary Analysis

The primary analysis will be conducted once the protocol and statistical analysis plan are finalized and approved.

9.6.2 Planned Method of Analysis

9.6.2.1 General Considerations

The statistical analysis in this study will be descriptive in nature. Categorical outcomes will be summarized by the number and percentage of subjects or events in each category. Continuous outcomes will be summarized by the number of nonmissing values, mean, standard deviation, median, lower and upper quartiles, minimum, and maximum.

9.6.2.2 Missing or Incomplete Data and Lost to Follow-up

All radiographic images, including those obtained prior to randomization to confirm the presence of bone metastases and skeletal surveys to determine the presence of fractures, were sent to RadPharm for review. In this study, analyses will be based on all analyzed imaging data provided by RadPharm. Missing data will not be imputed.

9.6.2.3 Descriptive Analysis

9.6.2.3.1 Description of Study Enrollment

All randomized subjects with solid tumors in Studies 20050103, 20050136, and 20050244 will be included. The subjects with multiple myeloma in Study 20050244 will be excluded from this study.

9.6.2.3.2 Description of Subject/Patient Characteristics

Demographics and baseline characteristics will be summarized for all randomized subjects with solid tumors, as well as for the subjects with any fractures.

9.6.2.4 Analysis of the Primary, Secondary and Exploratory Endpoint(s)

The event rates of metastatic and non-metastatic fractures (defined in Section 9.3.2) will be summarized descriptively by treatment for each study and for the integrated data. A subject may have multiple fractures. All pathologic fractures during the double blinded treatment period will be included in the analysis.

The event rates of vertebral and non-vertebral fractures (defined in Section 9.3.2) will be summarized using the similar method described above. Only non-metastatic fractures will be included in the analysis. For vertebral fractures, severity grade will be tabulated by treatment.

In addition to event rates, the subject incidence of any pathologic fractures, metastatic fractures, and non-metastatic fractures will be summarized by treatment. A subject may be included in both metastatic and non-metastatic fracture groups if the subject has multiple fractures. The incidence of fractures will be based on all randomized subjects with solid tumors. The incidence of metastatic and non-metastatic fractures will be based on all subjects with any pathologic fractures. Time to first metastatic fracture and time to first non-metastatic fracture will be analyzed.

The baseline medications known to affect bone density and/or history of osteoporosis will be summarized descriptively for subjects with at least 1 non-metastatic fracture.

The number of days on study and the total dose of investigational product will be summarized using descriptive statistics for the subjects with any fractures. A summary of proportion of subjects receiving each dose level (1 – 6, 7 – 12, 13 – 18, ≥ 19) will also be provided.

9.6.2.5 Sensitivity Analysis

Not Applicable

9.6.2.5.1 Subgroup Analysis

Not Applicable

9.6.2.5.2 Stratified Analysis

Not Applicable

9.6.2.5.3 Sensitivity Analysis for Residual Confounding and Bias

Not Applicable

9.6.2.5.4 Other Sensitivity Analysis

Not Applicable

9.6.3 Analysis of Safety Endpoint(s)/Outcome(s)

This is a retrospective analysis of already reported safety data. In this study safety data will not be collected.

9.7 Quality Control

Not Applicable

9.8 Limitations of the Research Methods

The location codes for bone metastases (Section 9.4) are more detailed than those for fractures. A limitation of this analysis is that if a bone metastasis is diagnosed in the same bone or area of a fracture, this will be recorded as a metastatic fracture.

A time-dependent association exists between fracture diagnosis and bone metastasis diagnosis in the same bone. For the purpose of this analysis, a time period of 6 months was applied. If a bone metastasis was diagnosed within 6 months after a fracture in the same bone, then this fracture is recorded as metastatic fracture

10. Protection of Human Subjects

Not Applicable

11. Collection, Recording and Reporting of Safety Information and Product Complaints

Not Applicable

11.1 Definition of Safety Events

All safety events have previously been reported and assessed.

12. Administrative and Legal Obligations

12.1 Protocol Amendments and Study Termination

Not Applicable.

13. Plans for Disseminating and Communicating Study Results

Results will be provided to the US FDA. No public disclosure of results is planned.

14. Compensation

Not Applicable

15. References

20050103 Clinical Study Report - A Randomized, Double-blind, Multicenter Study of Denosumab Compared With Zoledronic Acid (Zometa) in the Treatment of Bone Metastases in Men with Hormone-Refractory Prostate Cancer. 23 April 2010.

20050136 Clinical Study Report - A Randomized, Double-Blind, Multicenter Study of Denosumab Compared With Zoledronic Acid (Zometa) in the Treatment of Bone Metastases in Subjects with Advanced Breast Cancer. 29 October 2009.

20050244 Clinical Study Report - A Randomized, Double-Blind, Multicenter Study of Denosumab Compared With Zoledronic Acid (Zometa) in the Treatment of Bone Metastases in Subjects with Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma. 26 January 2010.

Aredia Summary of Product Characteristics; Aredia Prescribing Information. Available at http://emc.medicines.org.uk/medicine/7199/SPC/AREDIA+Dry+Powder+15mg%2c+30mg+and+90mg/ and http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=f00b6da7-3f74-4ef6-a1ac-343029cf97ea

Berenson JR, Lichtenstein A, Porter L, et al. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. *N Engl J Med*. 1996;334:488-493.

Body J-J. Rationale for use of bisphosphonates in osteoblastic and osteolytic bone lesions. *The Breast* 2003;Suppl 2:S37-S44.

Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. *Nature* 2003;423:337-42.

Buijs J, van der Pluijm G. Osteotropic cancers: from primary tumour to bone. *Cancer Lett* 2009;273:177-93.

Carlin BI, Andriole GL. The natural history, skeletal complications, and management of bone metastases in patients with prostate carcinoma. *Cancer*. 2000;88(12 Suppl):2989 2994.

Carlson RW, Allred DC, Anderson BO, et al. NCCN Clinical Practice Guidelines in Oncology, *Breast Cancer*, V.2.2011. National Comprehensive Cancer Network, Inc. Available at www.nccn.org.

Clark JCM, Dass CR, Choong PFM. Current and future treatments of bone metastases. *Expert Opin Emerging Drugs* 2008;13:609-27.

Clezardin P, Teti, A. Bone metastasis: pathogenesis and therapeutic implications. *Clin Exp Metastasis* 2007;24:599-608.

Coleman RE, Brown JE. Monitoring response to treatment – the role of biomarkers. In: Jasmin C, Coleman RE, Coia L, et al, eds. Textbook of Bone Metastases. Hoboken NJ: John Wiley and Sons; 2005b: p105.

Coleman RE, Guise TA, Lipton A, et al. Advancing treatment for metastatic bone cancer: consensus recommendations from the second Cambridge conference. *Clin Cancer Res* 2008;14:6387-95.

Coleman RE, Major P, Lipton A, et al. Predictive value of bone resorption and formation markers in cancer patients with bone metastases receiving the bisphosphonate zoledronic acid. *J Clin Oncol* 2005a;23:4925-35.

Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. *Clin Cancer Res* 2006;12(20 Suppl):6243s-49s.

Coleman RE. Skeletal complications of malignancy. *Cancer*. 1997;80:1588 1594.

Demers LM, Costa L, Lipton A. Biochemical markers and skeletal metastases. *Clin Orthop* 2003;415 (Suppl):S138-47.

DePuy V, Anstrom KJ, Castel LD, et al. Effects of skeletal morbidities on longitudinal patient-reported outcomes and survival in patients with metastatic prostate cancer. *Support Care Cancer*. 2007;15:869-876.

Elliott R, Kostenuik P, Chen C, et al. Denosumab is a selective inhibitor of human receptor activator of NF-κB ligand that blocks osteoclast formation in vitro and in vivo. *Eur J Ca Suppl* 2006;4:62.

Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner* Res. 1993;8:1137-1148

Gutta R, Louis PJ. Bisphosphonates and osteonecrosis of the jaws: science and rationale. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2007;104(2):186 193.

Hillner BE, Ingle JN, Chlebowski RT, et al. American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. *J Clin Oncol* 2003;21:4042-57.

Hortobagyi GN, Theriault RL, Porter L, et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. N Engl J Med 1996;335:1785-9.

Kleber M, Cybulla M, Bauchmüller K, et al. Monitoring of renal function in cancer patients: an ongoing challenge for clinical practice. *Ann Oncol*. 2007;18:950-958.

Kohno N, Aogi K, Minami H, et al. Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer: a randomized placebo-controlled trial. *J Clin Oncol* 2005;23:3314-21.

Kostenuik PJ, Nguyen HQ, McCabe J, et al. Denosumab, a fully human monoclonal antibody to RANKL, inhibits bone resorption and increases BMD in knock-in mice that express chimeric (murine/human) RANKL. *J Bone Miner Res*. 2009;24:182-195.

Lage MJ, Barber BL, Harrison DJ, Jun S. The Cost of Treating Skeletal-Related Events in Patients With Prostate Cancer. *Am J Manag Care*. 2008;14:317-322.

Launey-Vacher V, Gligorov J, Le Tourneau C, et al. Prevalence of renal insufficiency in breast cancer patients and related pharmacological issues. *Breast Cancer Res Treat* 2010;124 :745–753.

Roodman GD, Dougall WC. RANK ligand as a therapeutic target for bone metastases and multiple myeloma. *Cancer Treat Rev* 2008;34:92-101.

Roodman GD. Mechanisms of bone metastases. *New Engl J Med* 2004;350:1655-64.

Rosen LS, Gordon D, Kaminski M, et al. Zoledronic acid versus pamidronate for the treatment of bone metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. *Cancer J* 2001;7:377-87.

Rosen LS, Gordon DH, Dugan W, et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. *Cancer* 2004;100:36-43.

Rosen LS, Gordon G, Tchekmedyian S, et al. Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a Phase III, double-blind, randomized trial – The Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *J Clin Oncol* 2003;21:3150-7.

Roudier MP, Morrissey C, True LD, et al. Histopathological assessment of prostate cancer bone osteoblastic metastases. *J Urol*. 2008;180(3):1154-1160.

Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst* 2002;94:1458-68.

Selvaggi G, Scarlotti GV. Management of bone metastases in cancer: a review. *Crit Rev Oncol Hematol* 2005;56:365-78.

Theriault RL, Biermann JS, Brown E, et al. NCCN task force report: Bone health and cancer care. *J Natl Compr Canc Netw*. 2006;4 Suppl 2:S1-S20.

Theriault RL, Biermann JS, Brown E, et al. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. *J Clin Oncol* 1999;17:846-54.

Viadana E, Cotter R, Pickren JW, Bross IDJ. An autopsy study of metastatic sites of breast cancer. *Cancer Res*. 1973;33:179-181.

Warr D, Johnson M, Breast Cancer Disease Site Group. Use of bisphosphonates in women with breast cancer: practice guideline report #1-11 (version 2.2002). Hamilton ON: Cancer Care Ontario, Program in Evidence-based Care; 2004. Available at http://www.cancercare.on.ca/pdf/pebc1-11f.pdf.

Yonou H, Ochiai A, Goya M, et al. Intraosseous growth of human prostate cancer in implanted adult human bone: relationship of prostate cancer cells to osteoclasts in osteoblastic metastatic lesions. *Prostate*. 2004;58:406-413.

Zometa European Union Summary of Product Characteristics; Zometa US Prescribing Information. Available at http://emc.medicines.org.uk/medicine/14062/SPC/Zometa+4mg+5ml+Concentrate+for+Solution+for+Infusion/ and http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=f0cdfa57-95e5-416b-bc2f-cde2491c2fd0, respectively.

16. Appendices

Appendix A. List of Stand-alone Documents

No.	Document Reference Number.	Date	Title
1	*20050103*	*5 May 2008*	*Clinical Trial Protocol -A Randomized, Double-blind, Multicenter Study of Denosumab Compared With Zoledronic Acid (Zometa) in the Treatment of Bone Metastases in Men with Hormone-Refractory Prostate Cancer*
2	*20050136*	*15 August 2007*	*Clinical Trial Protocol - A Randomized, Double-Blind, Multicenter Study of Denosumab Compared With Zoledronic Acid (Zometa) in the Treatment of Bone Metastases in Subjects with Advanced Breast Cancer*
3	*20050244*	*7 March 2006*	*Clinical Trial Protocol - A Randomized, Double-Blind, Multicenter Study of Denosumab Compared With Zoledronic Acid (Zometa) in the Treatment of Bone Metastases in Subjects with Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma*

Appendix B. ENCePP Checklist for Study Protocols

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

Integrated Retrospective Analysis of Metastatic-related and Non metastatic-related Fractures in Studies 20050136, 20050244, and 20050103.

Study reference number:
20180024

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]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	

[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 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.5 Registration in the EU PAS register	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (eg, to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.2
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (ie, population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative 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? (eg, incidence rate, absolute risk)	☒	☐	☐	9.3.2
3.4 Does the protocol specify measure(s) of association? (eg, relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☒	☐	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (eg, adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:	☒	☐	☐	9.2.1
4.2.1 Study time period?	☐	☒	☐	
4.2.2 Age and sex?	☐	☒	☐	
4.2.3 Country of origin?	☒	☐	☐	9.2
4.2.4 Disease/indication?	☒	☐	☐	9.2.1
4.2.5 Duration of follow-up?				
4.3 Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☐	☐	☐	9.2.2.1

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? (eg, operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.6.2.4
5.2 Does the protocol address the validity of the exposure measurement? (eg, precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (eg, current user, former user, non-use)	☒	☐	☐	9.6.2.4
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

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?	☒	☐	☐	9.6.1
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.6.1
6.3 Does the protocol address the validity of outcome measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value,	☒	☐	☐	9.6.1

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
prospective or retrospective ascertainment, use of validation sub-study)				
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (eg, HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:				
7.2.1. Selection biases (eg, healthy user bias)	☐	☐	☒	
7.2.2. Information biases (eg, misclassification of exposure and endpoints, time-related bias)	☐	☐	☒	
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	

Comments:

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

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? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	9.4
9.1.2 Outcomes? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	9.4
9.1.3 Covariates?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
8.2.1 Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
8.2.2 Outcomes? (eg, date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
8.2.3 Covariates? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	9.3
9.3 Is a coding system described for:				
9.3.3 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
9.3.2 Outcomes? (eg, International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (eg, based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☐	☐	☐	9.6
10.2 Are descriptive analyses included?	☐	☐	☐	9.6
10.3 Are stratified analyses included?	☐	☐	☒	
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☐	☐	☐	9.6
10.6 Is sample size and/or statistical power estimated?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (eg, software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.4
11.2 Are methods of quality assurance described?	☐	☐	☒	

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

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?	☐	☐	☒	
12.1.2 Information bias?	☐	☐	☒	
12.1.3 Residual/unmeasured confounding? (eg, anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (eg, study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☒	

Comments:

Section 13: Ethical 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?	☐	☐	☒	

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 (eg, to regulatory authorities)?	☒	☐	☐	13

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	13

Comments:

Name of the main author of the protocol: PPD

Date: 05/03/2018

Signature: PPD