Summary Table of Study Protocol

Title	Postmarketing Surveillance Study of Prolia (Denosumab) in South Korea
Protocol version identifier	20160195
Date of last version of the protocol	NA
EU Post Authorisation Study (PAS) Register No	NA
Active Substance	Denosumab
Medicinal Product	Denosumab; Prolia®
Product Reference	NA
Procedure Number	NA
Marketing Authorisation Holder(s)	Amgen Korea Limited
Joint PASS	No
Research Question and Objectives	To estimate the incidence rates of adverse events and change in bone mineral density in patients being treated with Prolia® in a postmarketing setting as required by the Ministry of Food and Drug Safety.
Country(-ies) of Study	Republic of Korea
Author	[redacted]

Marketing Authorisation Holder

Marketing authorisation holder(s)	Amgen Korea Limited
MAH Contact	TBD

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Toll free number in South Korea: 00798 6113554

Amgen's general number in the United States: (1-805-447-1000)

Investigator's Agreement

I have read the attached protocol entitled Postmarketing Surveillance Study of Prolia (Denosumab) in South Korea dated 29 August 2016, and agree to abide by all provisions set forth therein.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Korea.

Signature	
Name of Investigator	Date (DD Month YYYY)

Study Design Schema

	Screening/Day 1[a]	Month 6	Last Visit/Month 12 (EOS)
Patient enrollment	X	-	-
Treatment with Prolia®	X	X	X
CRF (baseline)	X	-	-
CRF (follow-up)[b]	-	X	X
CRF (BMD)	X[c]	-	X
CRF (safety)	Reported according to study protocol (as data becomes available)		

BMD = bone mineral density; CRF = case report form; EOS = end of study.
[a] Screening and day 1 could occur on the same day.
[b] The frequency of follow-up visits, except for month 6 (provided the patient continues treatment with Prolia®), is at the discretion of the investigator.
[c] BMD value most proximal to start of Prolia®.

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2. List of Abbreviations

Abbreviation or Term	Definition/Explanation
ADT	androgen deprivation therapy
AIT	aromatase inhibitor therapy
BMD	bone mineral density
BMI	body mass index
CI	confidence interval
CRF	case report form
CRO	clinical research organization
CTx	cross-linked C-telopeptide
DXA	dual-energy x-ray absorptiometry
eCRF	electronic case report form
EDC	electronic data capture
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
End of study	defined as the date when the last patient is assessed or receives an intervention for evaluation in the study (ie, last patient last visit), following any additional parts in the study (eg, follow-up), as applicable. This definition also coincides with end of follow-up period.
End of study for an individual patient	defined as the last day that protocol-specified procedures are conducted for an individual patient
Enrollment	defined as the date the patient provides written consent and meets the inclusion criteria
EOS	end of study
EU	European Union
Follow-up period	up to 12 months starting from day 1 or until the patient expires or discontinues treatment
GFR	glomerular filtration rate
ICJME	International Committee of Medical Journal Editors
IRB	institutional review board
MAA	marketing authorization application
MFDS	Ministry of Food and Drug Safety

Abbreviation or Term	Definition/Explanation
NA	not applicable
PAS	postauthorization study
PI	Prescribing Information
PMS	postmarketing surveillance
Primary completion	defined as the date when the last patient is assessed for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary final analysis, whether the study concluded as planned in the protocol or was terminated early
Q6M	every 6 months
RANK	receptor activator of nuclear factor kappa-B
RANKL	receptor activator of nuclear factor kappa-B ligand
SC	subcutaneous
South Korea	The Republic of Korea
Study day 1	defined as the first day that protocol-required therapy (Prolia®) is/are administered to the patient (day 1 and enrollment could fall on the same day)
US	United States

3. Responsible Parties

Study Sponsor:	Amgen Korea Limited 14th Floor, 203, Teheran-ro, Gangnam-gu, Seoul Korea, Republic of Phone:

The list of investigators will be determined by which sites have access to Prolia® and can feasibly prescribe a reasonable number of patients. The list of investigators is at Amgen and is available upon request.

4. Abstract

- Study Title: Postmarketing Surveillance Study of Prolia (Denosumab) in South Korea
- Study Background and Rationale

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and susceptibility to fracture. Osteoporosis is one of the leading causes of significant morbidity and disability in the aging population and contributes to the increasing economic burden on the healthcare system. Previous studies have demonstrated the ability of denosumab to reduce bone turnover and additionally increase bone mineral density (BMD) regardless of sex, age, or menopausal status in women (Bone HG, 2008; Miller PD, 2008; Lewiecki EM, 2007; McClung MR, 2006). Denosumab (Prolia®) provides an opportunity for a safe, convenient, and effective therapeutic option with a rapid onset of action.

According to the Regulation on the Safety of Pharmaceuticals, etc, applicable to the products for which marketing authorization applications (MAAs) were submitted before 01 July 2015, a marketing authorization applicant in the Republic of Korea (South Korea) must conduct an observational postmarketing surveillance (PMS) study to characterize the safety and efficacy profiles in South Korean patients. A PMS study protocol must be submitted to the Ministry of Food and Drug Safety (MFDS) 1 month before the planned product launch in South Korea. The data from the PMS study will be included in the re-examination dossier. In addition, the findings will further develop and expand Prolia®'s already established global postmarketing safety profile.

Considering the need for progressive osteoporosis treatment options in South Korea and Prolia®'s current safety and efficacy profile, a PMS study on Prolia® in South Korea will not only satisfy local regulatory requirements but findings will reveal safety and efficacy in a population where denosumab is understudied.

In addition, according to local regulation, a regulatory PMS study is required for new medicines approved in South Korea to collect safety and efficacy data in a routine clinical practice. A prospective, observational, multicenter study design is chosen to meet the postmarket surveillance guidelines from the MFDS in South Korea.

- Research Question and Objective(s)
  - Primary Objective
    The primary objective of this study is to estimate the incidence rates of adverse

events, serious adverse events, and adverse drug reactions among patients receiving Prolia® in a postmarketing setting as required by the MFDS.

- Secondary Objective(s)
  The secondary objectives of this study are to:
  - investigate the efficacy of Prolia® by examining change in BMD at the lumbar spine.
  - investigate the efficacy of Prolia® by examining change in BMD of the total hip and femoral neck (if available).
  - describe characteristics (eg, demographics, medical history) of patients receiving Prolia® in the postmarketing setting.
- Hypothesis(es)/Estimation
  There is no hypothesis to be tested. Instead, the proposed study will provide descriptive data on the use of Prolia®, incidence of adverse events and adverse drug reactions, and BMD at the lumbar spine, total hip, and femoral neck, and patient characteristics in a postmarketing setting.

- Study Design/Type

This regulatory PMS study is a prospective, observational, multicenter study in patients who are being treated with Prolia®.

- Study Population or Data Resource

The goal of this study is to capture at least 3000 patients who are prescribed Prolia® in a clinical setting in South Korea for 12 months after their first dose of Prolia®.

- Summary of Patient Eligibility Criteria

Inclusion Criteria

- Patients who receive Prolia® (on-label) in the postmarketing setting in South Korea.
- Willing to provide access to previous and future medical information.
- Patients who consent to participate in this study.

Exclusion Criteria

- Patients unwilling to provide consent.
- Patients with hypocalcemia.
- Patients who are pregnant.
- Patients with known hypersensitivity to denosumab or any of its components.

- Follow-up

The duration of follow-up for each patient is 12 months from day 1. Administration of the first dose of Prolia® will occur on day 1.

- Outcome Variables
  - Primary Endpoint(s): Incidence of adverse events, serious adverse events, and adverse drug reactions.
  - Secondary Endpoint(s):
    - Percent change from baseline in BMD at 12 months (measured by dual-energy x-ray absorptiometry [DXA] scan) of the lumbar spine, total hip, and femoral neck.
    - Describe characteristics of patients receiving Prolia® in the postmarketing settting.
- Study Sample Size

Amgen will enroll at least 3000 patients to collect adequate safety and efficacy information for the final analysis at 12 months. A total of 3000 patients is large enough to rule out, with 95% exact confidence, an adverse event incidence rate greater than 0.12% if none is observed.

- Data Analysis

Descriptive analysis of the collected safety and efficacy endpoints will be conducted at interim analyses (every 6 months for the first 2 years from approval, then annually thereafter) and final analysis when all patients have the opportunity to complete the final study visit. No hypothesis testing will be performed. Categorical outcomes will be summarized by the number and percentage of subjects in each category. Continuous outcomes will be summarized by the number of nonmissing values, mean, standard deviation, median, lower and upper quartiles, and minimum and maximum values. For the incidence, 95% confidence interval (CI) will be presented based on an exact method. The analysis will include all enrolled patients (enrollment is triggered once an eligible, consenting patient receives their first dose of Prolia®).

5. Amendments and Updates

None.

6. Milestones

Milestone	Planned date
Start of data collection	October 2016
End of data collection	January 2020
Periodic report 1-1	Submitted
Periodic report 1-2	Submitted
Periodic report 2-1	Submitted
Periodic report 2-2	Submitted
Periodic report 3	November 2017
Periodic report 4	November 2018
Periodic report 5	November 2019
Registration in the EU PAS register	Before first-in-patient
Final report of study results	December 2020

7. Rationale and Background

7.1 Diseases and Therapeutic Area

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and susceptibility to fracture. Osteoporosis risk increases with age and women are more likely than men to develop osteoporosis, particularly during the postmenopausal period. Other risk factors include Caucasian and Asian ethnicity, family history, low calcium and vitamin D intake, smoking, and alcohol intake. Androgen deprivation therapy (ADT), aromatase inhibitor therapy (AIT), and long-term use of glucocorticoids and/or some anticonvulsants also increase the risk of bone loss.

Osteoporosis is one of the leading causes of significant morbidity and disability in the aging population and contributes to the increasing economic burden on the healthcare system. According to the 2008-2011 Korea National Health and Nutrition Examination Survey, the prevalence of osteoporosis in South Korea was 7.3% in males (n = 3414) and 38.0% in females (n = 4011) ≥ 50 years of age (Park et al, 2014). Bisphosphates are the most commonly prescribed drugs to treat osteoporosis in South Korea, but despite a 3-fold increase in prescriptions between 2008-2013 osteoporotic fractures did not significantly decrease. Drug compliance and disease awareness might be a reason for reduced efficacy in individual patients; however, prior to October 2011 medical reimbursement guidelines in South Korea only covered 6 months of osteoporosis treatment and required a T-score of < -3.0 or a history of osteoporosis-related fractures of the hip or spine. Since October 2011, reimbursement guidelines changed to

12 months of coverage with a T-score of -2.5 after an annual bone mineral density (BMD) assessment (Lee et al, 2013). These changes have demonstrated that the risk of mortality and socioeconomic burden of osteoporosis in South Korea justify the need for effective treatments.

Previous studies have demonstrated the ability of denosumab to reduce bone turnover and additionally increase BMD in postmenopausal women (Bone, 2008; Lewiecki, 2007; McClung, 2006; Miller, 2008). In 2 different studies (20040138 and 20040135), denosumab given as 60-mg subcutaneous (SC) injections every 6 months significantly improved BMD ($p < 0.0001$) as compared with placebo in subjects with prostate (Study 20040138) or breast cancer (Study 20040135). In the prostate cancer study (20040138), denosumab significantly reduced the incidence of new vertebral fractures through month 36 by 62.0% (relative risk, 0.38; 95% CI, 0.19 to 0.78; adjusted $p = 0.0125$). The subject incidence of new vertebral fracture through month 36 was 1.5% (10/679 subjects) in the denosumab group and 3.9% (26/673 subjects) in the placebo group. In the breast cancer study (20040135), 8 subjects (6%) in each group reported nonvertebral fractures and no vertebral fractures were reported during the 24-month treatment period. Kaplan-Meier estimates of the risk of nonvertebral fracture were 3.3% for the denosumab group and 3.5% for the placebo group at month 12 and 7.2% for both treatment groups at month 24.

Osteoporosis presents a major public health issue as the world's population ages. The morbidity and mortality associated with osteoporotic-related fractures is devastating in terms of disability to an individual and cost to the global economy. Denosumab provides an opportunity for a safe, convenient, and effective therapeutic option with a rapid onset of action.

Denosumab is a fully human monoclonal antibody that binds with high affinity (dissociation equilibrium constant [K_d] 3×10^{-12} M) and specificity to receptor activator of nuclear factor kappa-B ligand (RANKL) which neutralizes the activity of RANKL, thereby preventing activation of its receptor, receptor activator of nuclear factor kappa-B (RANK), on the surface of precursor and mature osteoclasts. As a consequence, bone resorption is reduced. Denosumab has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian Chinese hamster ovary cells. It consists of 2 heavy chains of the immunoglobulin G2 subclass and 2 light chains of the kappa subclass which are covalently linked through disulfide bonds. Prolia® is formulated for SC injection and is administered at a dose of 60 mg every 6 months (Q6M) for bone loss

indications. Prolia® is colorless to slightly yellow, clear to slightly opaque, and practically free from particle injectable solution in a colorless and clear prefilled syringe. Administration will be in accordance with the Korean Prolia® Prescribing Information (PI).

Prolia® is currently indicated for the treatment of postmenopausal women with osteoporosis, treatment of men with osteoporosis, treatment of bone loss in men receiving ADT for prostate cancer, and the treatment of bone loss in women receiving AIT for breast cancer.

7.2 Rationale

According to the Regulation on the Safety of Pharmaceuticals, etc, applicable to the products for which marketing authorization applications (MAAs) were submitted before 01 July 2015, a marketing authorization applicant in the Republic of Korea (South Korea) must conduct an observational postmarketing surveillance (PMS) study to characterize the safety and efficacy profiles in South Korean patients. A PMS study protocol must be submitted to the Ministry of Food and Drug Safety (MFDS) 1 month before the planned product launch in South Korea. The data from the PMS study will be included in the re-examination dossier. In addition, the findings will further develop and expand Prolia®'s already established global postmarketing safety profile.

Considering the need for progressive osteoporosis treatment options in South Korea and Prolia®'s current safety and efficacy profile, a PMS study on Prolia® in South Korea will not only satisfy local regulatory requirements but findings will reveal safety and efficacy in a population where denosumab is understudied.

In addition, according to local regulation, a regulatory PMS study is required for new medicines approved in South Korea to collect safety and efficacy data in a routine clinical practice. A prospective, observational, multicenter study design is chosen to meet the postmarket surveillance guidelines from the MFDS in South Korea.

7.3 Statistical Inference (Estimation or Hypothesis[es])

This regulatory PMS is a prospective, observational, multicenter study in patients who are being treated with Prolia®. There is no hypothesis to be tested. Instead, the proposed study will provide descriptive data on use of Prolia®; the incidence of adverse events and adverse drug reactions; BMD at the lumbar spine, total hip, and femoral neck; and patient characteristics in the postmarketing setting.

8. Research Question and Objectives

8.1 Primary

The primary objective of this study is to estimate the incidence rates of adverse events, serious adverse events, and adverse drug reactions among patients receiving Prolia® in a postmarketing setting as required by the MFDS.

8.2 Secondary

The secondary objectives of this study are to:

- investigate the efficacy of Prolia® by examining BMD at the lumbar spine.
- investigate the efficacy of Prolia® by examining BMD of the total hip and femoral neck (if available).
- describe characteristics (eg, demographics, medical history) of patients receiving Prolia® in the postmarketing setting.

9. Research Methods

9.1 Study Design

This is a prospective, observational, multicenter study in patients who are being treated with Prolia® in the postmarketing setting in South Korea. No study drug will be provided by Amgen Korea. There will be no control group. Since osteoporosis is a common condition, it seems prudent to capture adverse events with frequencies as low as 1 in 1000. The goal of this study is to capture at least 3000 patients who are prescribed Prolia® in the South Korea. If patients meet the inclusion criteria (Section 9.2.3.1) and sign the informed consent, they will be considered enrolled. All data collected for the purpose of this study will be extracted from the information generated or gathered through routine medical practice.

The enrollment period will stop after approximately 2 years when the enrolled sample size is at least 3000. This will allow 12 months follow-up of the last enrolled patient, analysis, and reporting in preparation for re-examination by the MFDS. Each patient will be followed from the first dose of Prolia® until the end of the 12-month period, death, or loss to follow-up (eg, patients transferring to another clinic), whichever occurs first.

9.1.1 General Study Procedures

Table 1 presents the schedule of assessments and study procedures.

9.1.1.1 Patient Background Information

At baseline, the following patient characteristics and parameters will be collected by using structured case report forms (CRFs):

- Osteoporosis diagnosis: etiology (type of osteoporosis or indication for which Prolia® is prescribed) and disease duration
- Physical exam: height and weight
- Demographics: sex and age
- Medical history of disease (for prior therapies include therapy name, indication, dose, unit, frequency, route of administration, and start and stop date):
    - history of drug allergies
    - fracture history (prevalent fractures, site of prevalent fracture, number of prevalent vertebral fractures)
    - renal impairment (chronic kidney disease, estimated glomerular filtration rate [GFR])
    - hepatic impairment (Child-Pugh class A, B, or C)
    - prior use of calcium and/or vitamin D
    - prior use of bisphosphate preparations
    - prior use of other osteoporosis treatment(s)
    - serum calcium and vitamin D levels
    - other medical conditions associated with the safety and efficacy of Prolia® therapy for the patients
        - including conditions and drug treatments that influence bone metabolism
        - history of dental procedures (checklist of relevant conditions to be provided in CRF)
- Concomitant medications including therapy name, indication, dose, unit, frequency, route of administration, and start and stop date will be collected:
    - Concomitant use of calcium and/or vitamin D
    - Concomitant use of bisphosphate preparations
    - Concomitant use of other osteoporosis treatment(s)
- Lifestyle variables: smoking (past and present), alcohol consumption, and exercise.

9.1.1.2 Laboratory Values

Clinical laboratory values will be collected at baseline and during other routine visits as deemed necessary by the investigator and processed locally (serum creatinine, liver function, parathyroid hormone, cross-linked C-telopeptide [CTx], serum calcium level, and vitamin D levels should be collected at baseline; and serum calcium and CTx should also be collected when available during regular clinical visits).

9.1.1.3 Safety Data

For the safety assessment, all adverse events are collected on day 1 and as they become available throughout the follow-up period. Standardized CRFs will be used for reporting.

9.1.1.4 Treatment Status

Treatment continuation or discontinuation will be assessed using end of treatment CRFs. If discontinued, the reason for discontinuation (ie, safety event, disease progression, death, or loss to follow-up) will be documented. This form should be collected upon treatment discontinuation or completion at the last visit.

9.1.1.5 BMD

BMD will be measured using dual-energy x-ray absorptiometry (DXA) scans and processed locally during routine clinical visits. Method of assessment will be per the site's clinical standard for measuring BMD of the lumbar spine, total hip, and femoral neck. Measurement method, model of measuring device, and specific site of measurement will be collected. BMD will be reported using structured CRFs.

Table 1. Schedule of Assessments

	Screening[a] (Start of Prolia®)	Follow-up Visits [b,c] (Surveillance Period, Early Termination Visit)	Last Visit[b] /EOS
Data Collection	Day 1	Month 6	Month 12
Eligibility	X	-	-
Informed consent	X	-	-
Physical exam	X	-	-
Laboratory values[b]	X	-	-
Medical history	X	-	-
Demographic data	X	-	-
Concomitant medications	X	X	X
Osteoporosis diagnosis	X	-	-
Lifestyle variables	X	X	X
Treatment status	-	X	X
Treatment with Prolia®	X	X	X
DXA (lumbar spine and proximal total hip)[d]	X[e]	-	X
Safety data	X	X	X

BMD = bone mineral density; CA = calcium; CTx = cross-linked C-telopeptide; DXA = dual-energy x-ray absorptiometry; EOS = end of study.
[a] Screening and day 1 could take place on the same day.
[b] The frequency of follow-up visits (including collection of laboratory values such as serum CA and CTx), except for month 6 (provided the patient continues treatment with Prolia®), is at the discretion of the investigator. Frequency after the initial visit is not specified as this depends on the investigator's clinical decision for each patient.
[c] Visit should occur within ±4 weeks.
[d] Total hip and femoral neck will be collected if available.
[e] BMD value most proximal to start of Prolia® and within past 6 months.

9.2 Setting and Study Population

The study population comprises patients treated with Prolia® in a clinical setting which includes any primary through tertiary healthcare setting where Prolia® is prescribed. Patients will be screened for eligibility, receive a single dose of Prolia® during their initial visit/day 1 (which could be the same day as screening), and return for follow-up visits at the discretion of the investigator based on the patient's course of treatment. According to the Korean Prolia® PI, Prolia® is administered every 6 months; thus, patients who remain on treatment will have up to 2 follow-up visits during the 12-month follow-up period (defined below).

9.2.1 Study Period

Definitions

- Enrollment: Defined as the date the patient provides written consent and meets the inclusion criteria (see Section 9.2.3.1).
- Study day 1: Defined as the first day that protocol-required therapy (Prolia®) is administered to the patient (day 1 and enrollment could fall on the same day).
- Follow-up period: Up to 12 months starting from day 1 or until the patient expires or discontinues treatment.
- End of study: Defined as the date when the last patient is assessed or receives an intervention for evaluation in the study (ie, last patient last visit, following any additional parts in the study [eg, long-term follow-up]), as applicable. This definition also coincides to end of follow-up period.
- End of study for an individual patient: Defined as the last day that protocol-specified procedures are conducted for an individual patient.
- Primary completion: Defined as the date when the last patient is assessed for the final collection of data for the primary endpoint(s), for the purposes of conducting the final analysis, whether the study concluded as planned in the protocol or was terminated early.
- Final analysis period: Beginning early 2020.

9.2.2 Selection and Number of Sites

Sites will be eligible to participate in the study if they are listed among the sites to receive and administer Prolia® according to the formulary and can feasibly prescribe a reasonable number of patients. Approximately 40 sites will be enrolled to participate.

9.2.3 Subject/Patient Eligibility

9.2.3.1 Inclusion Criteria

- Patients who receive Prolia® (on-label) in the postmarketing setting in South Korea.
- Willing to provide access to previous and future medical information.
- Patients who consent to participate in this study.

9.2.3.2 Exclusion Criteria

- Patients unwilling to provide consent.
- Patients with hypocalcemia.
- Patients who are pregnant.
- Patients with known hypersensitivity to denosumab or any of its components.

9.2.4 Study Follow-up

The duration of follow-up for each patient is 12 months from day 1. Administration of the first dose of Prolia® will occur on day 1.

9.3 Variables

9.3.1 Outcome Assessment

9.3.1.1 Primary Endpoint

Incidence of adverse events and adverse drug reactions (including seriousness and causality to drug), inclusive of reaction at local injection sites, will be collected as they become available throughout the follow-up period and reported. Subject level incidence will be reported and summarized by classification according to the adverse event coding.

9.3.1.2 Secondary Endpoints

- Percent change from baseline in BMD at 12 months (measured by DXA scan) of the lumbar spine, total hip, and femoral neck.
- Describe characteristics of patients receiving Prolia® in the postmarketing setting.

9.3.2 Validity and Reliability

Efforts will be made to collect complete data through the use of clear instructions to investigators regarding the completion of CRFs.

9.4 Data Sources

Patient data will be collected by investigators or site staff at routine clinical visits or as reported in between visits by the patient and captured on the electronic CRF (eCRF). The investigator or site staff will ask specific questions of the patients to assess for any potential occurrence of safety events. BMD will be collected by DXA per the site's clinical standard of measurement. All laboratory values will be transferred from the local/onsite laboratory to the Amgen database.

9.5 Study Size

Amgen will enroll at least 3000 patients to collect adequate safety and efficacy information for the final analysis at 12 months. A total of 3000 patients is large enough to rule out, with 95% exact confidence, an adverse event incidence rate greater than 0.12% if none is observed. At this number, it is expected that known severe side effects of Prolia® will be detected in $\geq$ 1 patient.

9.6 Data Management

Standard Amgen processes for clinical trial and data management will be used in this study.

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the patient's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Patient files containing completed CRFs, informed consent forms, and patient identification list.
- Study files containing the protocol with all amendments, copies of prestudy documentation, and all correspondence to and from the institutional review board (IRB) and Amgen.

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available. Retention of study documents will be governed by the PMS Agreement.

9.6.1 Obtaining Data Files

Not applicable.

9.6.2 Linking Data Files

Not applicable.

9.6.3 Review and Verification of Data Quality

Data quality is reviewed and verified through logical check and queries are made to the sites, when needed.

9.7 Data Analysis

9.7.1 Planned Analyses

9.7.1.1 Interim Reports

Data will be summarized in each periodic PMS report according to the schedule described in Section 6 (Milestones).

9.7.1.2 Final Analysis

The final analysis will be conducted when all patients have the opportunity to complete the last protocol-specified assessment in the study.

9.7.2 Planned Method of Analysis

9.7.2.1 General Considerations

The statistical analysis in this PMS study will be descriptive in nature and no hypothesis testing will be performed. Categorical outcomes will be summarized by the number and percentage of subjects in each category. Continuous outcomes will be summarized by the number of nonmissing values, mean, standard deviation, median, lower and upper quartiles and minimum and maximum values. For the incidence, 95% confidence interval (CI) will be presented based on an exact method.

9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

Patients may have missing data points for a variety of reasons. Data may be missing due to patient's early withdrawal from study, a missed visit, or nonevaluability of an endpoint at a particular time point. In general, analyses will be based on available data. Sensitivity analyses may be conducted using different approaches to handle missing data. Missing baseline and postbaseline BMD data will not be imputed.

9.7.2.3 Descriptive Analysis

9.7.2.3.1 Description of Patient Characteristics

Demographic and baseline characteristics collected (see Section 9.1.1.1) will be tabulated descriptively.

9.7.2.4 Analysis of the Primary and Secondary Endpoint(s)

Incidence Rates of Adverse Events and Adverse Drug Reactions

The analysis will be based on the safety analysis set which includes all enrolled subjects (enrollment is triggered once an eligible, consenting patient receives their first dose of Prolia®). The incidence of adverse events will be summarized by classification according to the adverse event coding dictionary. This summary includes all treatment-emergent adverse events recorded from the start of investigational product on this study, or any worsening of adverse events initially experienced before initiation of this study. This summary for adverse events will be performed for the following categories:

- All adverse events and adverse drug reactions
- Prolia®-related adverse events
- Serious adverse events and serious drug reactions
- Prolia®-related serious adverse events
- Adverse events leading to Prolia® therapy discontinuation
- Fatal events

The incidence of adverse events of interest will be presented and if applicable, 95% CI for the incidence estimate using an exact method will be provided.

In addition to the quantitative analysis, medical assessment of the characteristics of individual adverse events and adverse drug reaction by safety physicians and pharmacovigilance scientists will be conducted.

BMD Changes

Percent change (%) in BMD from baseline at lumbar spine will be analyzed. Patients with baseline and at least 1 postbaseline assessment will be included in the analysis.

Percent change (%) in BMD from baseline at total hip and femoral neck will be analyzed (if available). Patients with baseline and at least 1 postbaseline assessment will be included in the analysis.

9.7.2.4.1 Subgroup Analysis

- The primary and secondary endpoints will be analyzed by the following subgroups if appropriate:
  - Sex (females vs males)
  - Age at baseline (years)
  - Osteoporosis diagnosis (postmenopausal osteoporosis, bone loss due to ADT, or bone loss AI therapy)
  - History of osteoporosis therapy use (prior and/or concomitant bisphosphonate or other treatment use)
  - Male osteoporosis
  - Body mass index (BMI) at baseline
  - Renal function at baseline (stage of chronic kidney disease based on estimated GFR)
  - Hepatic impairment (Child-Pugh class A, B, or C) at baseline

9.8 Quality Control

The Amgen representative(s) and regulatory authority inspectors are responsible for inspecting the various records of the study (eg, CRFs and other pertinent data) provided that patient confidentiality is respected.

The Amgen or Clinical Research Organization (CRO) staff is responsible for verifying the CRFs to verify adherence to the protocol, completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of PMS studies.

The investigator agrees to cooperate with Amgen or CRO staff to ensure that any problems detected in the course of the study, including delays in completing CRFs, are resolved.

In accordance with the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing function (or designees).

9.9 Limitations of the Research Methods

9.9.1 Internal Validity of Study Design

9.9.1.1 Measurement Error(s)/Misclassification(s)

As with any surveillance study that relies on data entry from multiple sites, there is the potential for misclassifying adverse events and adverse drug reactions (including seriousness and causality). Misclassifications can impact the validity of outcomes as well as affect overall conclusions.

9.9.1.2 Information Bias

Missing or incomplete data is a potential risk for information bias and efforts will be made to collect complete data through the use of clear instructions to investigators regarding the completion of CRFs. Information about patient diagnosis will be collected, so data can be interpreted separately between on-label and off-label use of Prolia®. Amgen will list potential sites/investigators who may prescribe Prolia® in the postmarketing setting. Based on the list, Amgen will check interest and willingness of the potential investigator(s) to participate in this surveillance. Based upon the results, sites who participate in this study will be confirmed.

9.9.1.3 Selection Bias

Selection bias limitations include lack of a control group, failure to adhere to protocol-specified enrollment criteria, and a small sample size. As such, this can affect the assessment and evaluation of the impact of the treatment.

To limit the selection bias, at least 3000 patients who receive Prolia® treatment in the postmarketing setting in South Korea are expected to enroll; all known Prolia® prescribing physicians will be offered an opportunity to participate in the study (if a physician does not want to join the study, it will be documented by Amgen).

9.9.1.4 Confounding

It is very likely that patients enrolled in this study (ie, patients with bone loss who receive Prolia®) are more severely diseased than patients with bone loss who do not receive Prolia® (and thus are not included in the study). This confounding by indication bias will limit the ability of any safety and efficacy results to be generalized to the larger indicated population.

9.9.1.5 Reporting Bias

There is no systematic review or systematic method of adverse event collection. Adverse events are collected as part of a regular interaction with the patient as would be in normal practice. Therefore, adverse events collected are subject to reporting bias, but such effect is inherent to real-world surveillance.

9.9.2 External Validity of Study Design

DXA scans for BMD are only covered once per year by insurance. As such, inadequate or lack of BMD data could impact the breadth of data necessary to make generalizations about the source population.

9.9.3 Limitations Due to Missing Data and/or Incomplete Data

Some patients may drop out of the study, creating missing or incomplete data for the study endpoint assessments. Such dropout may be related or informative to the outcomes. Consequently, there is a risk for bias and lack of robust data to analyze results.

9.10 Other Aspects

9.10.1 Language

All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood.

10. Protection of Human Subjects

10.1 Informed Consent

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Clinical Study Manager to the investigator. The written informed consent document is to be prepared in the language(s) of the potential patient population.

Before a patient's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the patient/patient's parent or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational product(s) is/are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical study.

The investigator is also responsible for asking the patient/patient's parent if the patient has a primary care physician and if the patient/patient's parent agrees to have his/her primary care physician informed of the patient's participation in the clinical study. If the patient/patient's parent agrees to such notification, the investigator is to inform the patient's primary care physician of the patient's participation in the clinical study. If the patient does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the patient's medical record.

The acquisition of informed consent and the patient/patient's parent agreement or refusal of his/her notification of the primary care physician is to be documented in the patient's medical records, and the informed consent form is to be signed and personally dated by the patient/patient's parent or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the patient or legally acceptable representative. If a potential patient/patient's parent is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the patient/patient's parent and must allow for questions. Thereafter, both the patient/patient's parent and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

10.2 Institutional Review Board (IRB)

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of patients into the study.

The investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator is responsible for obtaining annual IRB approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB continuance of approval must be sent to Amgen.

10.3 Patient Confidentiality

The investigator must ensure that the patient's confidentiality is maintained for documents submitted to Amgen.

- Patients are to be identified by a unique patient identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the CRF demographics page, in addition to the unique patient identification number, include the age at time of enrollment.
- For serious adverse events reported to Amgen, patients are to be identified by their unique patient identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

Authorized representatives of Korea Amgen Limited, the regulatory agency(s), and the IRB shall have direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the patient to permit such individuals to have access to his/her study-related records, including personal information.

10.4 Patients' Decision to Withdraw

Patients have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Withdrawal of consent for a study means that the patient does not wish to or is unable to continue further study participation. Patient data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data can be included after withdrawal of consent. The investigator is to discuss with the patient appropriate procedures for withdrawal from the study.

10.5 Regulatory Authority

By the current regulation, a draft protocol for a Prolia® regulatory PMS observational study must be provided to the MFDS at least 1 month before launching the product in South Korea. The MFDS will review and approve the study protocol within 1 month from submission unless revisions are requested by the MFDS.

Amgen will report safety data arising from this study to regulatory authorities in accordance with safety reporting guidelines and in compliance with applicable local regulations. Safety data from this study may be reportable to regulatory authorities outside of South Korea.

11. Collection of Safety Information and Product Complaints

Adverse events, product complaints, and other safety findings, such as pregnancy and lactation cases, will be collected and reported in this study. Investigators should also follow appropriate local and postmarketing reporting requirements.

11.1 Definition of Safety Events

11.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product(s) irrespective of a causal relationship with this treatment.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product(s), whether or not considered related to the product(s). The definition of an adverse event includes:

- worsening of a pre-existing condition or underlying disease.
- events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms).

It is the investigator's responsibility to evaluate whether an adverse event is related to an Amgen product prior to reporting the adverse event to Amgen.

An adverse device effect is any adverse event related to the use of a medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device (ie, prefilled syringe), or adverse events resulting from use error or from intentional misuse of the device.

11.1.2 Serious Adverse Events

A serious adverse event is any adverse event as defined above that meets at least one of the following serious criteria:

- is fatal
- is life-threatening (places the patient at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity

- is a congenital anomaly/birth defect
- is an "other significant medical hazard" that does not meet any of the above criteria

A hospitalization meeting the regulatory definition for "serious" is any in-patient hospital admission that includes a minimum of an overnight stay in a healthcare facility.

"Other significant medical hazards" refer to important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

11.1.3 Other Safety Findings

Other safety findings (regardless of association with an adverse) include:

- medication errors, overdose, whether accidental or intentional, misuse, or abuse involving an Amgen product,
- pregnancy and lactation exposure,
- transmission of infectious agents,
- reports of uses outside the terms for authorized use of the product including off-label use,
- occupational exposure, or
- any lack or loss of intended effect of the product(s).

11.1.4 Product Complaints

Product complaints include any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product or device after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. This includes any drug(s) or device(s) provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.

Amgen will collect complaints on the following product:

- Prolia® 60 mg prefilled syringe

Product complaints may include but are not limited to issues related to:

- Appearance (eg, broken, cracks, color, particles, odor)
- Labeling (eg, missing, torn, smudged)

- Durability (eg, stability issues)
- Open packaging
- Device damage (eg, prefilled syringe with bent needle)
- Inability of customer to understand product labeling
- Inability of customer to deliver the product successfully, including partial or
- incomplete delivery (eg, defective delivery system [syringe])

11.2 Safety Reporting Requirements

The investigator is responsible for ensuring that safety events (adverse events, product complaints, and other safety findings) observed by the investigator or reported by the patient that occur during the predetermined data collection period are recorded in the patient's appropriate study documentation and CRF. Serious adverse events and pregnancy and lactation cases must be submitted as individual case safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper or electronic form) within 1 business day of investigator awareness.

If the electronic data capture (EDC) system is used and unavailable to the site staff to report the adverse event, the information is to be reported to Amgen via a paper Adverse Event Contingency Report Form (Appendix A). For EDC studies where the first notification of an Adverse Event is reported to Amgen via the Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

See Appendix B for sample Safety Report Form(s), Appendix C for Additional Safety Reporting Information regarding the adverse event grading scale used in this study, and Appendix D for sample Pregnancy and Lactation Notification Worksheets.

The investigator may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded on study CRFs where safety data may also be recorded (eg, Event CRF).

11.2.1 Safety Reporting Requirement to Regulatory Bodies

Amgen will report safety data as required to regulatory authorities, investigators/institutions, IRBs, or other relevant ethical review board(s) in accordance with pharmacovigilance guidelines and in compliance with local regulations. The investigator is to notify the appropriate IRB or other relevant ethical review board of serious adverse events in accordance with local procedures and statutes.

12. Administrative and Legal Obligations

12.1 ENCePP Checklist for Study Protocols

Appendix E provides a sample checklist for the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).

12.2 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the investigator must be obtained where applicable per local governing law and/or regulations. The IRB must be informed of all amendments and give approval. The investigator **must** send a copy of the approval letter from the IRB or other relevant ethical review board to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the investigator reserve the right to terminate the investigator's participation in the study according to the contractual agreement. The investigator is to notify the IRB or other relevant ethical review board in writing of the study's completion or early termination and send a copy of the notification to Amgen.

13. Plans for Disseminating and Communicating Study Results

Interim results are included in periodic safety update reports due to the MFDS, and final results will be included in an application for re-examination.

13.1 Publication Policy

The results of this study have the potential for being published as a conference presentation and/or manuscript.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3, and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.

- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

14. Compensation

Participating sites will be compensated in accordance with fair market value for PMS studies in South Korea.

15. References

Amgen Inc. A randomized, double-blind, placebo-controlled study to evaluate AMG 162 in the treatment of bone loss in subjects undergoing androgen-deprivation therapy for nonmetastatic prostate cancer. Clinical Study Report 20040138, 15 October 2008.

Amgen Inc. A randomized, double-blind, placebo-controlled study to evaluate AMG 162 in the treatment of bone loss in subjects undergoing aromatase inhibitor therapy for nonmetastatic breast cancer. Clinical Study Report 20040135, 17 November 2008.

Amgen Korea Limited. Korea Prolia Prescribing Information: Pre-filled Syringe (Denosumab 60 mg) 15 March 2016.

Bone HG, Bolognese MA, Yuen CK, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. *J Clin Endocrinol Metab*. 2008;93:2149-2157.

Lee YK, Yoon BH, Koo KH. Epidemiology of Osteoporosis and Osteoporotic Fractures in South Korea. *Endocrinol Metab*. 2013;28:90-93.

Lewiecki EM, Miller PD, McClung MR, et al. Two-year treatment with denosumab (AMG 162) in a randomized phase 2 study of postmenopausal women with low BMD. *J Bone Miner Res*. 2007;22:1832-1841.

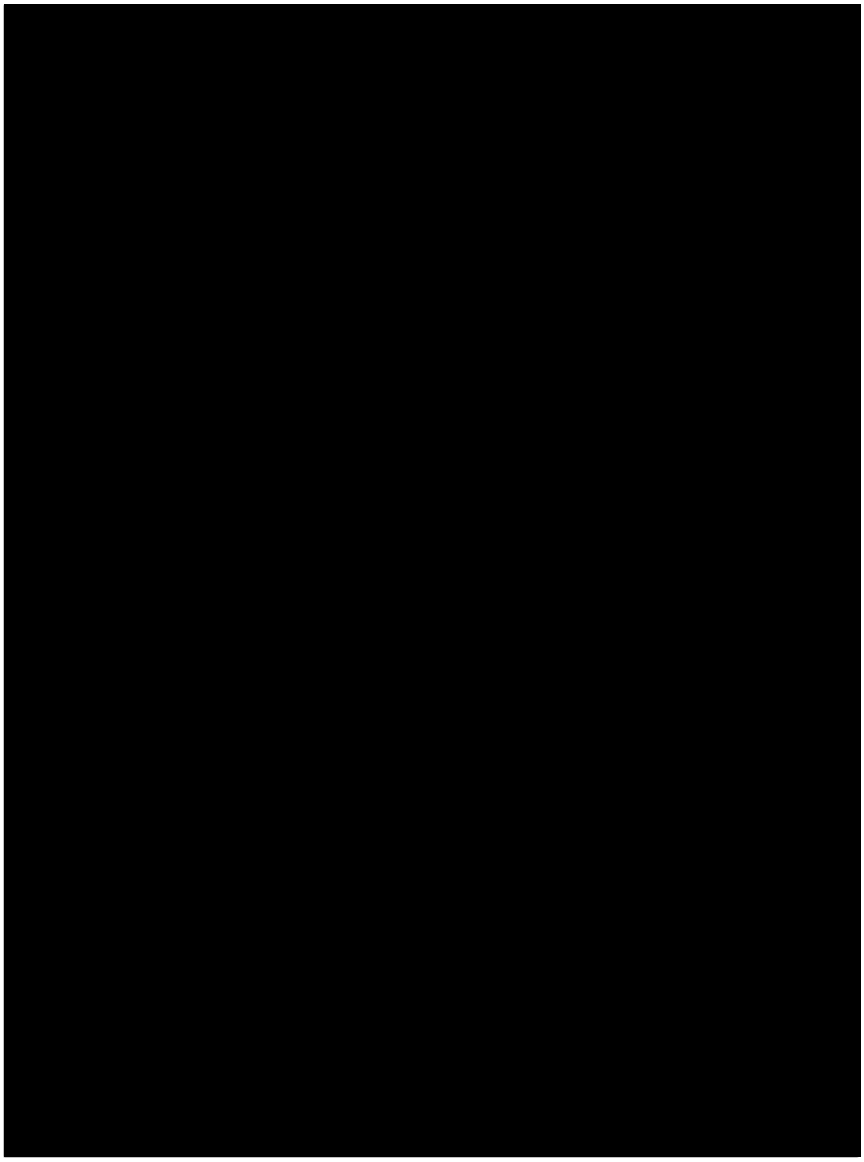
McClung MR, Lewiecki EM, Cohen SB, et al. Denosumab in postmenopausal women with low bone mineral density. *N Engl J Med*. 2006;354:821-831.

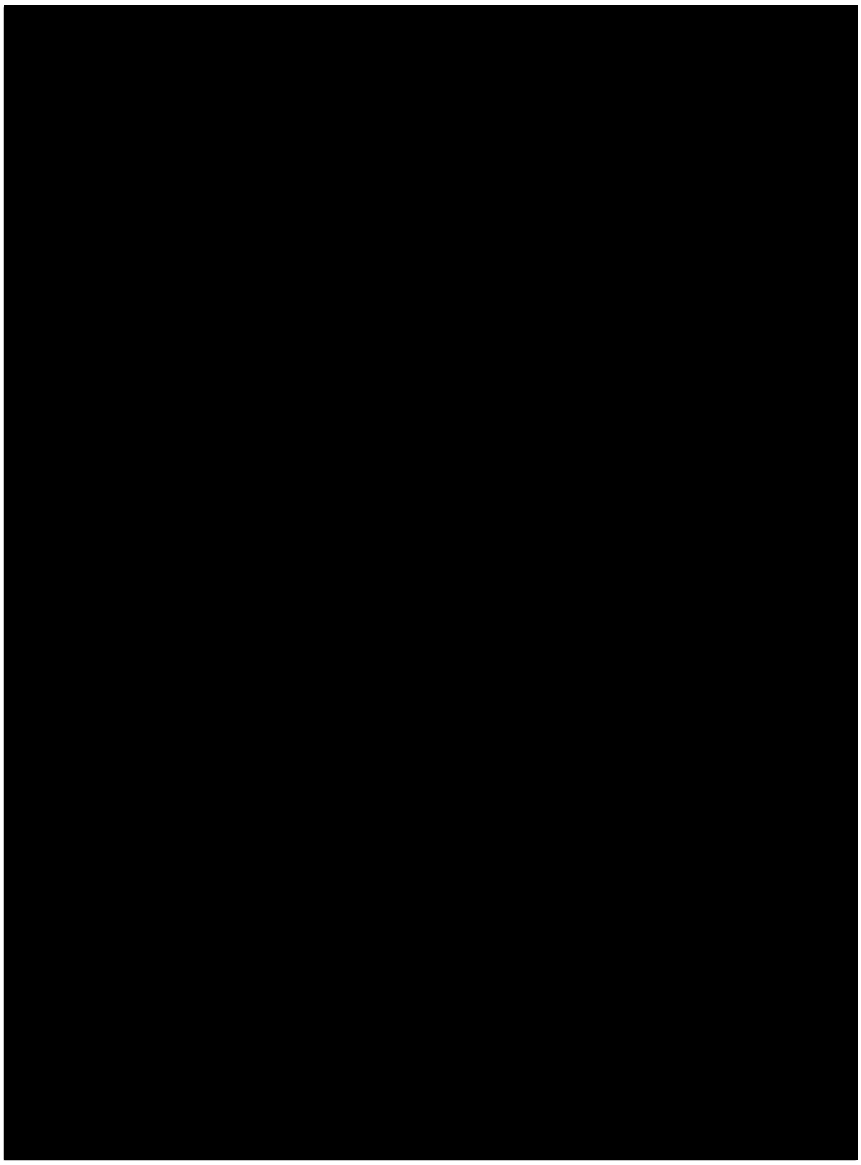
Miller PD, Bolognese MA, Lewiecki EM, et al. Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. *Bone*. 2008;43:222-229.

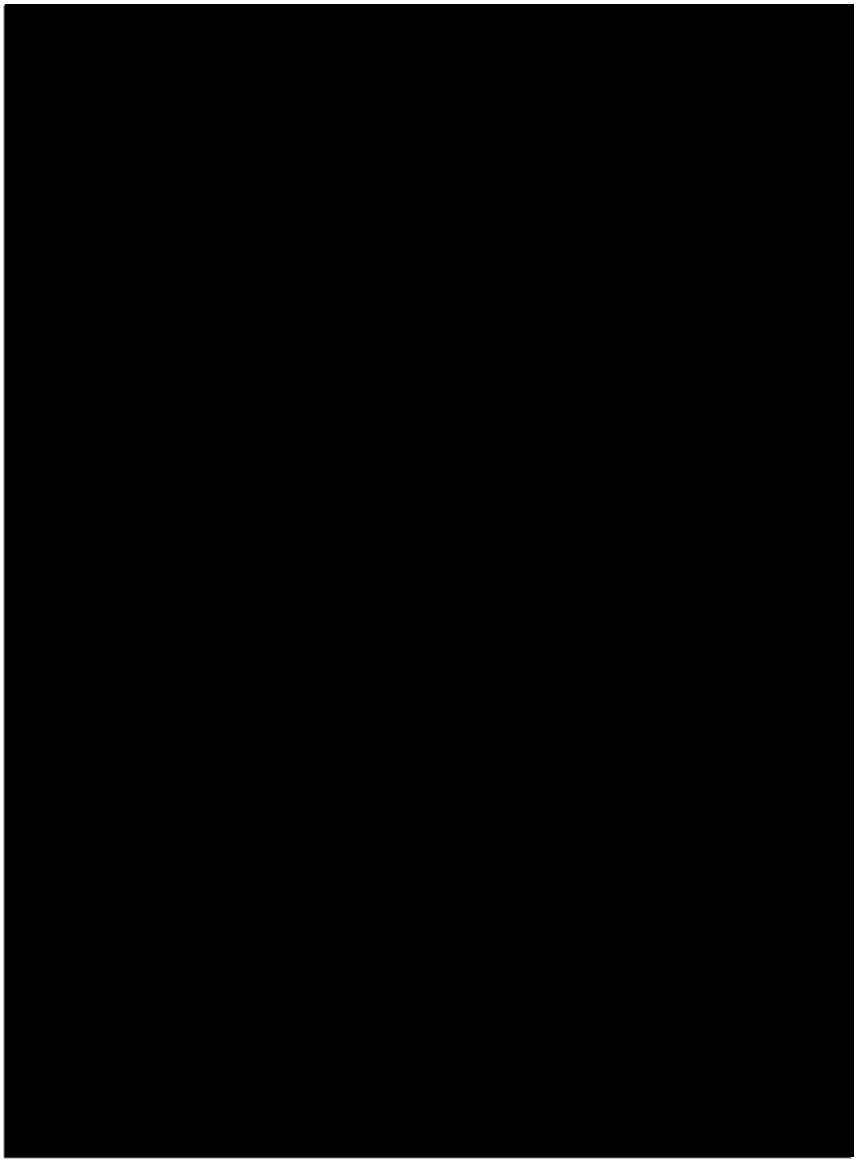
Park EJ, Joo IW, Jang MJ, Kim YT, Oh K, Oh HJ. Prevalence of Osteoporosis in the Korean Population Based on Korea National Health and Nutrition Examination Survey (KNHANES), 2008—2011. *Yonsei Med J*. 2014;55(4):1049-1057.

16. Appendices

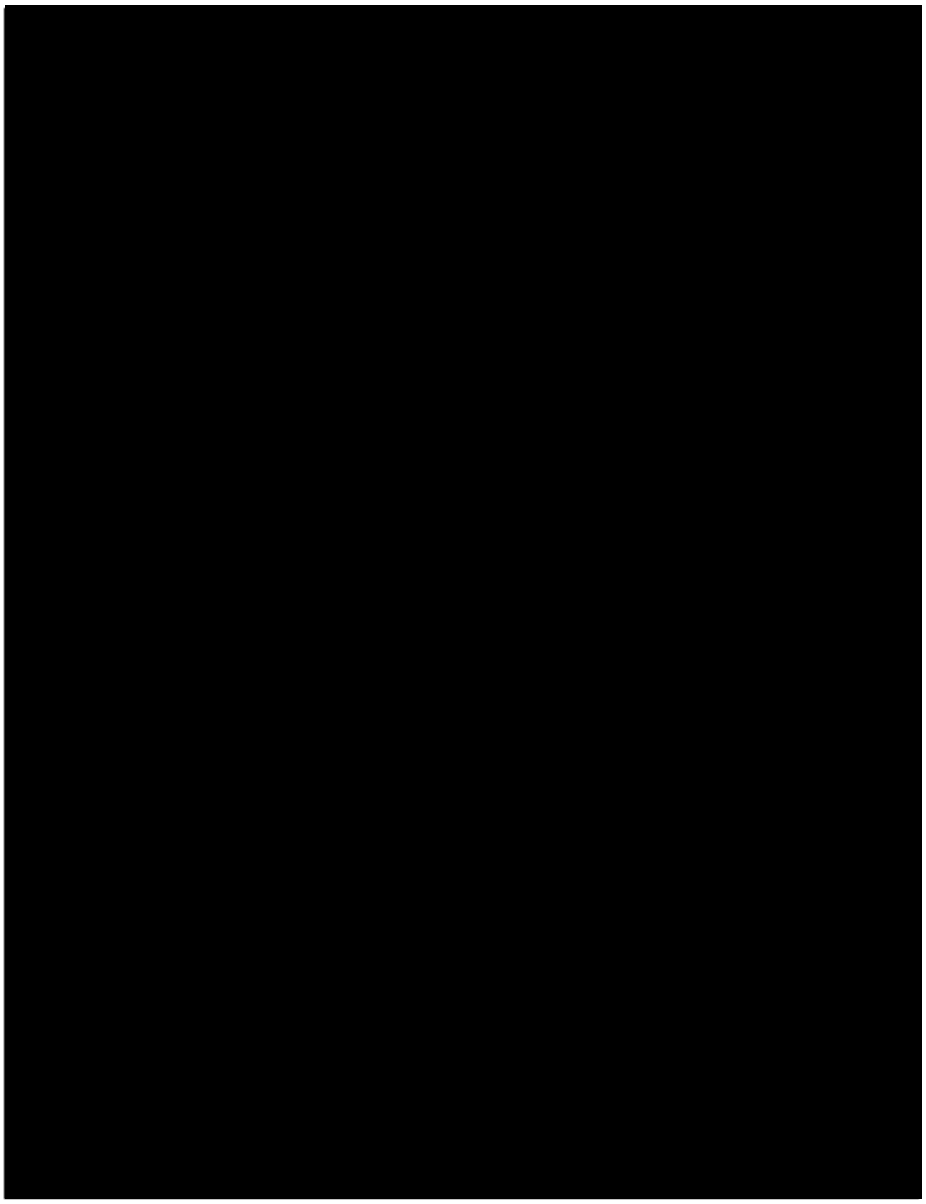
Appendix A. Adverse Event Contingency Report Form







Appendix B. Sample Safety Reporting Form(s)



Appendix C. Additional Safety Reporting Information

Adverse Event Severity Scoring System

When reporting an adverse event, include the severity assessed according to the following definitions:

- Mild: There are subjective and/or objective symptoms which do not interfere with the patient's normal daily activities. The treatment with Prolia® is continued without its dose change.
- Moderate: There are symptoms which interfere with the patient's normal daily activities. Dose reduction of Prolia® or other intervention for adverse event treatment is required.
- Severe: There are symptoms which prevent the normal daily activities. Discontinuation of Prolia® is required.

Relationship to Prolia®

(1) Certain

An event occurring in a plausible time relationship to use/administration of the drug, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug should be clinically plausible. The event must be definitive pharmacologically or phenomenologically using a re-challenge procedure if necessary.

(2) Probable/likely

An event with a reasonable time relationship to use/administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (re-challenge information not available).

(3) Possible

An event with a reasonable time relationship to use/administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

(4) Unlikely

A temporary occurrence which makes a causal relationship to use/administration of the drug improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

(5) Conditional/unclassified

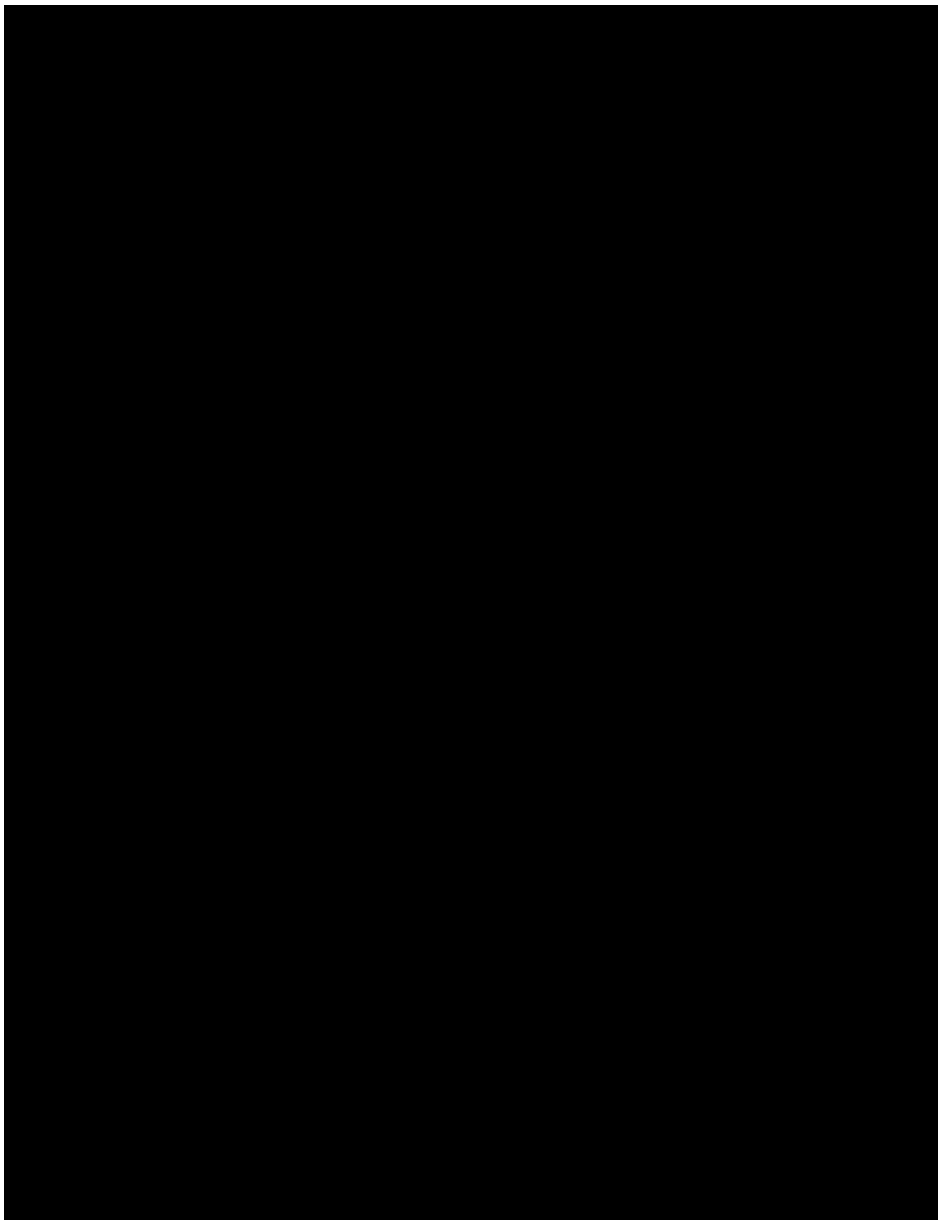
An event about which more data are essential for a proper assessment or the additional data are under examination.

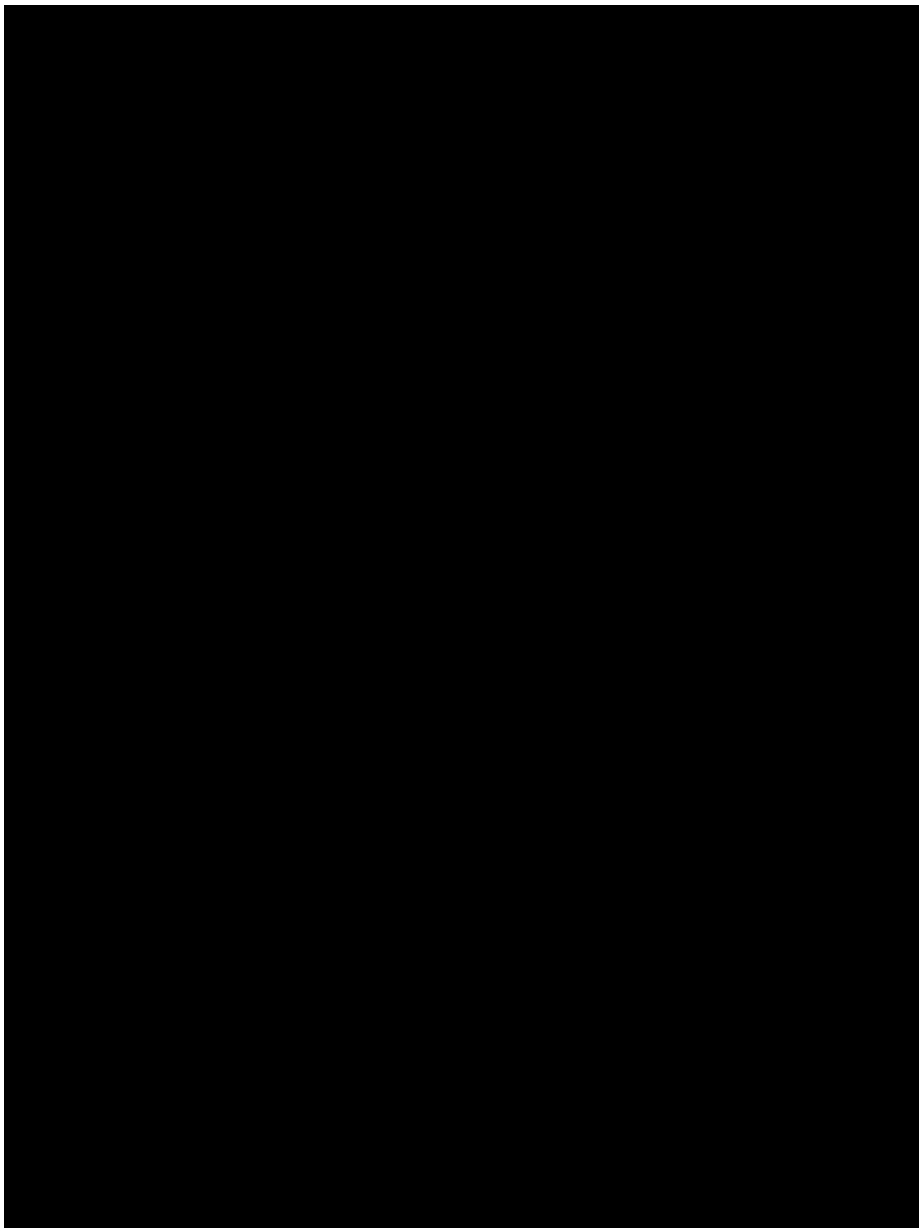
(6) Unassessable/unclassifiable

An event which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

For the reporting purposes, it is considered that the events assessed “unlikely” has no reasonable possibility of a causal relationship between the event and Prolia®.

Appendix D. Pregnancy and Lactation Notification Worksheets





Appendix E. Sample ENCePP Checklist for Study Protocols

Study title:

Study reference number:

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

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? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☐	☐	☐	
2.1.2 The objective(s) of the study?	☐	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☐	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☐	

Comments:

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

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☐	☐	☐	
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☐	☐	☐	
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☐	☐	☐	
3.4 Does the protocol specify measure(s) of association? (e.g. 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? (e.g. 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?	☐	☐	☐	
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☐	☐	☐	
4.2.2 Age and sex?	☐	☐	☐	
4.2.3 Country of origin?	☐	☐	☐	
4.2.4 Disease/indication?	☐	☐	☐	
4.2.5 Duration of follow-up?	☐	☐	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☐	☐	☐	

Comments:

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

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☐	
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?	☐	☐	☐	
6.2 Does the protocol describe how the outcomes are defined and measured?	☐	☐	☐	
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☐	
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. 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 (e.g. healthy user bias)	☐	☐	☐	
7.2.2. Information biases (e.g. 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? (e.g. 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? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☐	☐	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☐	☐	☐	
9.1.3 Covariates?	☐	☐	☐	
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☐	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☐	
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☐	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☐	
9.3.2 Outcomes? (e.g. 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? (e.g. 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?	☐	☐	☐	
10.2 Are descriptive analyses included?	☐	☐	☐	
10.3 Are stratified analyses included?	☐	☐	☐	

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☐	
10.5 Does the plan describe methods for handling missing data?	☐	☐	☐	
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? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☐	☐	
11.2 Are methods of quality assurance described?	☐	☐	☐	
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? (e.g. 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? (e.g. 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?	☐	☐	☐	

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
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?	☐	☐	☐	

Comments:

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

Comments:

Name of the main author of the protocol: _____

Date: dd/Month/year

Signature:_____