Summary Table of Study Protocol

Title	Periodic Knowledge, Attitudes, and Behavior (KAB) Survey of Certified Prescribers to Assess Understanding of the Risks with the Prolia Risk Evaluation and Mitigation of Strategy (REMS)
Protocol version identifier	Prolia 20240121 Version 1.0
Date of last version of the protocol	15 August 2024
EU Post Authorization Study (PAS) Register No	
Active Substance	Denosumab
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Device	NA
Product Reference	NA
Procedure Number	NA
Joint PASS	No
Research Question and Objectives	The objectives of the Healthcare Provider (HCP) KAB Survey are to conduct a survey with HCPs who are currently prescribing and have the potential to prescribe Prolia. The following key risk messages will address how this survey will be utilized to ensure the REMS is meeting its goal. HCPs must understand the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD) (estimated glomerular filtration rate [eGFR[redacted] (Key Risk Message 1). HCPs must understand the need to assess for presence of chronic kidney disease-mineral bone disorder (CKD-MBD) before initiating Prolia (Key Risk Message 2). HCPs must understand the requirement to provide each Prolia patient, a copy of the Patient Guide (Key Risk Message 3). The survey will begin with screening questions followed by key risk message questions. Additionally, the survey will collect data about HCP awareness, receipt, review/reading, and use of the Prolia educational materials followed by the collection of demographic information.
Country(ies) of Study	United States

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Marketing Authorization Holder

Marketing authorization holder(s)	Amgen Inc.
MAH Contact	PPD, Global Safety Director, Amgen Inc.

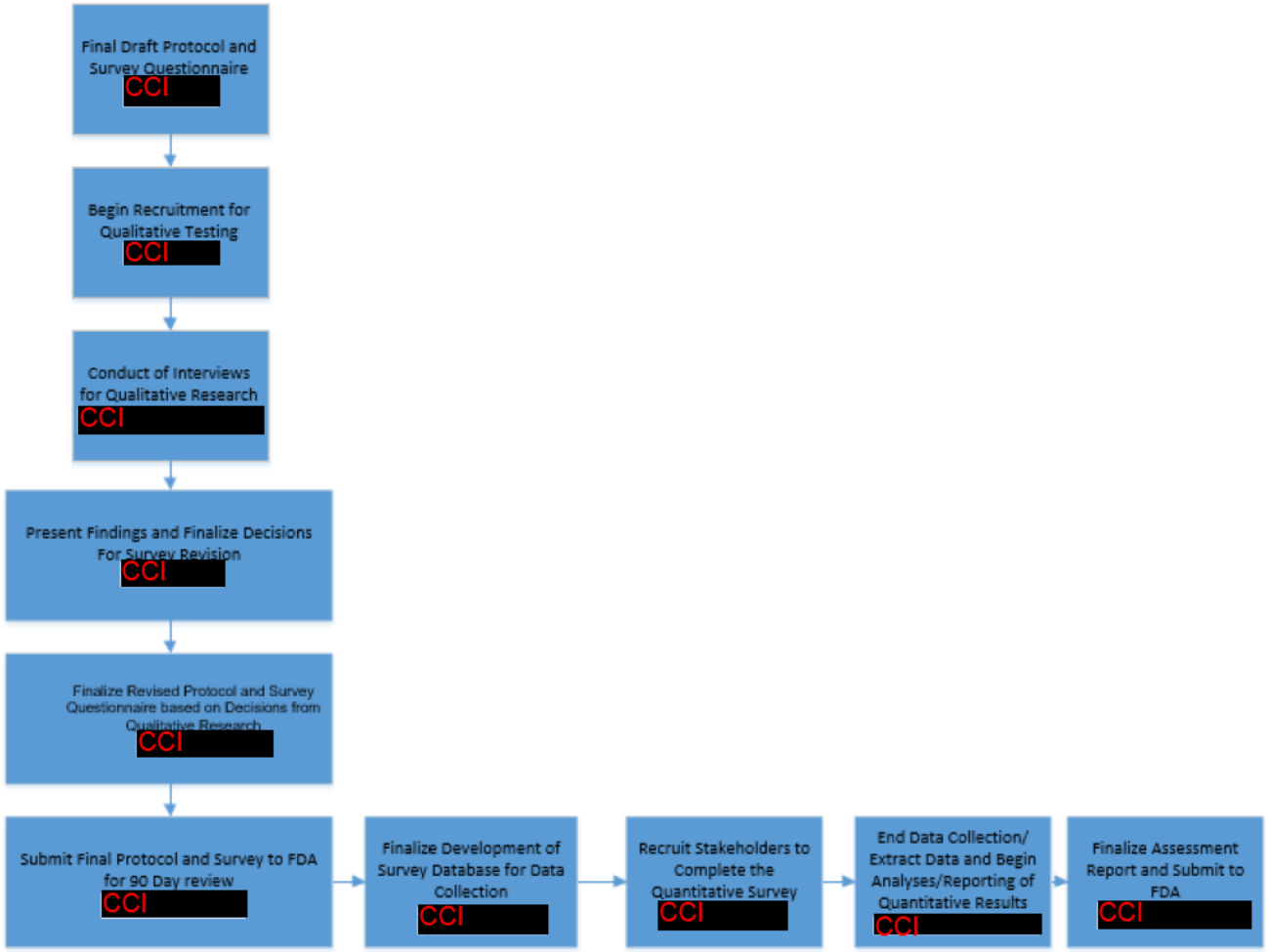
This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

Protocol Version	Date of Protocol	Page Header Date
Original, Version 1.0	15 August 2024	15 August 2024

Confidentiality Notice

Study Design Schema

Wave 1 KAB Survey Projected Timeline



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2. List of Abbreviations

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
Amgen	Amgen Inc.
APRN	Advanced Practice Registered Nurse
CAPTCHA	Completely Automated Public Turing Test to Tell Computers and Humans Apart
CFR	Code of Federal Regulations
CI	Confidence Interval
CKD	Chronic Kidney Disease
CKD-MBD	Chronic Kidney Disease-Mineral Bone Disorder
CNP	Certified Nurse Practitioner
CNS	Clinical Nurse Specialist
DCT	Data Collection Tool
DO	Doctor of Osteopathy
eGFR	Estimated Glomerular Filtration Rate
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
FDCA	Food, Drug, and Cosmetic Act
GCP	Good Clinical Practice
HCP	Healthcare Provider/Professional
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG2	Immunoglobulin G2
iPTH	Intact Parathyroid Hormone
IRB	Institutional Review Board
KAB	Knowledge, Attitudes, and Behavior
MD	Doctor of Medicine
N/A	Not Applicable

Abbreviation	Definition
NPI	National Provider Identifier
OSF	Other Safety Events
OH	Hydroxy
PA	Physician Assistant
QC	Quality Control
RANK	Receptor Activator of Nuclear Factor-Kappa B
RANKL	RANK Ligand
QR	Qualitative Research
QR Code	Quick Response Code
REMS	Risk Evaluation and Mitigation Strategy
SAS	Statistical Analysis System
SCC	Survey Coordinating Center
SERRM	Safety, Epidemiology, Registries & Risk Management
SOP	Standard operating procedure
TL	Tables and Listings
UAT	User Acceptance Testing
UBC	United BioSource LLC
URL	Uniform Resource Locator
US	United States
USPI	United States Prescribing Information

3. Responsible Parties

Name, Degree(s)	Job Title	Affiliation	Address
PPD , JD	Assoc Director | REMS Planning & Implementation Lead	Amgen Inc.	One Amgen Center Drive Thousand Oaks, CA 91320
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4. Abstract

Title: Prolia Periodic Knowledge, Attitudes, and Behavior (KAB) Survey of healthcare providers (HCPs) to Assess Understanding of the Risks with the Prolia Risk Evaluation and Mitigation of Strategy (REMS)

Study Background and Rationale: The Prolia™ REMS was originally approved on 01 June 2010, and the Food and Drug Administration (FDA) notified Amgen Inc. (hereafter referred to as Amgen) on 19 January 2024 that a REMS modification was required. Further, the United States (US) FDA accepted Amgen's proposed REMS, submitted on 02 February 2024, and formally approved it on 05 March 2024. The modified REMS consists of a communication plan and a timetable for submission of assessments of the REMS. In accordance with section 505-1 of Federal Food, Drug, and Cosmetic Act (FDCA), the FDA determined that a REMS is necessary for Prolia to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD) and chronic kidney disease-mineral bone disorder (CKD-MBD) and to educate HCPs regarding:

the need to assess the presence of CKD-MBD before initiating Prolia.

a) their understanding of the requirement to provide each Prolia patient with a copy of the Patient Guide.

The specific objectives to be achieved by the Prolia REMS include the assessment of HCPs knowledge of:

a) Risk of severe hypocalcemia in patients with advanced CKD (estimated glomerular filtration rate [eGFR] CCI [redacted]
b) Need to assess for presence of CKD-MBD before initiating Prolia
c) Requirement to provide each Prolia patient with a copy of the Patient Guide

The survey will begin with screening questions followed by key risk message questions. The survey will also collect data about HCP awareness, receipt, review/reading, and use of the Prolia educational materials followed by the collection of demographic information.

A component of the Prolia REMS Assessment Plan is the conduct of a quantitative evaluation survey with HCPs who are currently prescribing (hereafter referred to as the "HCP KAB Survey"), and those who have the potential to prescribe Prolia, to assess awareness of the REMS materials, knowledge of the risks associated with Prolia, and knowledge of the requirements of the Prolia REMS. Findings from the HCP KAB Survey, together with other REMS evaluation metrics, will be used to assess the Prolia

REMS and determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the intended goal.

This protocol provides the procedures to be followed with HCPs who are currently prescribing and those who have the potential to prescribe Prolia, who have not been debarred or otherwise sanctioned, for inclusion in the Prolia REMS Assessment Reports to be submitted to the FDA at 18 months (Wave 1), 3 years (Wave 2), and 7 (Wave 3) years post the approval of the modified REMS. This noninterventional study is part of the Prolia REMS Assessment and is a commitment to the FDA.

Research Question(s) & Objective(s): The objectives of the HCP KAB survey are to conduct a survey with HCPs who are currently prescribing and those who have the potential to prescribe Prolia, who are part of the REMS Communication Plan outreach, and who have not been debarred or sanctioned in order to assess their awareness and understanding of the risk of severe hypocalcemia with Prolia, the Prolia REMS requirements, and the REMS goals and materials. The key risk messages to support the objectives are as follows:

- Key Risk Message 1: HCPs must understand the risk of severe hypocalcemia in patients with advanced CKD (estimated glomerular filtration rate [eGFR] CCI
- Key Risk Message 2: HCPs must understand the need to assess for presence of CKD-MBD before initiating Prolia.
- Key Risk Message 3: HCPs must understand the requirement to provide each Prolia patient with a copy of the Patient Guide.

The survey questions associated with each key risk message have been developed as described above. Select survey questions were pre-tested through qualitative research (QR) and finalized prior to implementation of the Wave 1 of the HCP KAB Survey.

Study Design: This is a US-based, observational, cross-sectional survey of HCPs who are currently prescribing and those who have the potential to prescribe Prolia and who have not been debarred or otherwise sanctioned. The survey can be self-administered by the respondents via secure internet and telephone modalities utilizing a validated United BioSource LLC (UBC) Knowledge Survey System for data collection that is secure for receiving and storing survey data.

In an effort to ensure maximum participation in the survey, all HCPs identified at a designated interval, prior to survey launch, will receive a Pre-Notification Letter explaining the purpose and details of the upcoming survey. After the Pre-Notification

Letter has been sent, upon launch of the survey, the HCP targeted population will be sent an Invitation Letter. Throughout the survey wave, reminder letters will be distributed to non-responders. Outbound calling may also be engaged based on survey uptake and availability of telephone numbers.

Population:

HCPs must meet all of the following inclusion criteria will be included in the study:

- HCPs identified via Amgen's database, who are currently prescribing and those who have the potential to prescribe Prolia, who are part of the REMS Communication Plan outreach will be permitted to participate.
- HCPs who have not been debarred or otherwise sanctioned will be permitted to participate.
- HCPs who have participated in QR will be permitted to participate.[1]

Prolia HCPs meeting any of the following exclusion criteria will not be included in the study:

- Respondents who do not agree to participate in the survey.
- Respondents who are currently working for and/or whose immediate family members who are currently working for or are a consultant to Amgen, UBC, or the FDA.
- Respondents who report having a conflict of interest.

Given the gap in time between survey data collection, past completers will be permitted to participate in multiple waves. To monitor knowledge across the past completers and new completers, a sub-group analysis will be implemented by key risk message for both the primary and secondary analyses (Section 8.7.9).

Variables: The HCP KAB Survey will document each participant's knowledge and assess the attitudes and behaviors of the important information as presented in the key risk messages communicated through the Prolia REMS. Select survey questions will be pre-tested via QR and submitted for FDA review on or before 30 September 2024.

The HCP KAB Survey will also collect demographic characteristics for HCPs who complete all survey questions.

1. Because of the time in which this qualitative evaluation takes place compared to when the quantitative survey is conducted, allowing those who participated in QR to also participate in the quantitative survey creates no inherent risk in influencing the outcome of whether or not the Prolia HCPs are aware of the REMS objectives.

These include:

- Medical degree of respondent
  - Doctor of Medicine (MD), Doctor of Osteopathy (DO), Physician Assistant (PA), Advanced Practice Registered Nurse (APRN) including Certified Nurse Practitioner (CNP), Clinical Nurse Specialist (CNS).
- Medical Specialty
- Number of patients being treated with Prolia
- Length of time working as an HCP
- Prescriber versus Non-Prescriber
- Past Completer versus Current Completer (beginning with Wave 2)
- Geographic location
- Survey completion status

Eligibility and reasons for ineligibility will be presented by counts and percentages.

Data Sources: The survey will be administered via a secure web-based internet connection, which will allow respondents who choose to participate to do so at a time and location that is convenient for them.

The structured survey comprises questions or statements written in several formats, which include specific key risk messages:

- Questions or statements with a defined list of possible answers from which the respondent is required to choose one answer (ie, multiple-choice).
- Questions or statements with a defined list of possible answers from which the respondent is required to choose one or more answers (eg, “Select all that apply”).
- Questions or statements with response options of “yes” or “true,” “no” or “false,” and “I don’t know” that require the respondent to indicate agreement or disagreement.

All answers for questions or statements will be tallied to provide a broad picture of the respondent’s knowledge, attitudes, and behavior.

The desired response for key risk messages is generally “true” or “yes” indicating knowledge of the objectives of the Prolia REMS. However, some questions are formatted to have the respondent disagree with the statement as written (“false” or “no”) to avoid having the same affirmative answer for all desired responses. Whenever possible within a key risk message, there will be an equal balance of questions with a “true” or “yes” and “false” or “no.”

The recruitment list for survey participation will be derived from Amgen’s database. This list will include HCPs who are currently prescribing and those who have the potential to

prescribe Prolia, who are part of the REMS Communication Plan outreach, and who have not been debarred or sanctioned. The HCP characteristics that are captured in this dataset to be used for survey execution includes the HCPs first name, last name, medical specialty, National Provider Identifier (NPI) number, state medical license number, state of practice, facility name, and mailing address. Any additional contact information (ie, e-mail address/telephone number/fax number) may be retrieved from an external source prior to survey launch.

Study Size: The survey will target the completion of at least 371 completed surveys in Wave 1.

Data Analysis: Statistical analyses will be primarily descriptive in nature. Survey administration data will be described using descriptive statistics.

In the primary analysis, descriptive analyses will be performed for each key risk message question. For each question/item, the number of individuals who selected each response will be reported. Additionally, the percentage and 95% confidence interval (CI) will be calculated for the correct response.

Milestones: Data collection for Wave 1 will begin in March 2025. The 18-month assessment report will be submitted to the FDA by 05 September 2025. The Assessment Reports will continue at Wave 2 (Year 3) and Wave 3 (Year 7) with data collection ending on 05 January 2031 and the final assessment report submitted to FDA by 05 March 2031.

Milestones

Milestones	Planned Date[1]
Final Study Protocol and Survey	CCI
Start of Data Collection	
Wave 1 Assessment Report due to FDA	
Wave 2 Assessment Report due to FDA	
Wave 3 Assessment Report due to FDA	
End of Data Collection	TBD[2]
Final Assessment Report	TBD[2]

1. Dates are subject to change based on receipt of FDA feedback.
2. The Assessment Reports will continue until notified otherwise by the FDA. In the year of the Final Assessment Report, data collection will end on 05 January 2031 and the final assessment report will be submitted by 05 March 2031.

Objectives	Endpoints
Primary	
To describe HCP knowledge of: • The risk of severe hypocalcemia in patients with advanced CKD (eGFR[redacted] • The need to assess for presence of CKD-MBD before initiating Prolia • The understanding of the requirement to provide each Prolia patient with a copy of the Patient Guide	The number of HCPs who provide at least 80% or more correct responses for at least 80% of the overall questions for each key risk message.
Secondary	
Not Applicable (N/A)	Not Applicable (N/A)
Exploratory	
Not Applicable (N/A)	Not Applicable (N/A)

CKD = chronic kidney disease; CKD-MBD = chronic kidney disease-mineral bone disorder; eGFR = estimated glomerular filtration rate; HCP = healthcare provider; N/A = not applicable

- Study Design/Type

This is a US-based, observational, cross-sectional survey of HCPs identified via Amgen's database, who are currently prescribing and those who have the potential to prescribe Prolia, who are part of the REMS Communication Plan outreach, and who have not been debarred or sanctioned will be permitted to participate. The survey can be self - administered by the respondents via secure internet and telephone modalities utilizing a validated UBC Knowledge Survey System for data collection that is secure for receiving and storing survey data.

- Study Population or Data Resource

All HCPs who are currently prescribing and those who have the potential to prescribe Prolia will be eligible for participation.

- Summary of Respondent Eligibility Criteria

HCPs must meet all the following inclusion criteria to be included in the study:

  - Who are currently prescribing and those who have the potential to prescribe Prolia.
  - Who are part of the REMS Communication Plan outreach.
  - Who have not been debarred or sanctioned.

HCPs meeting any of the following criteria will not be included in the study:

- Respondents who do not agree to participate in the survey.
- Respondents who are currently working for and/or whose immediate family members are currently working for or as a consultant to Amgen, UBC, or the FDA.
- Respondents who report having a conflict of interest.

- Follow-up

  Not Applicable (N/A)

- Variables

The key risk messages, which will be evaluated in this KAB survey, include the following:

Key Risk Message 1: HCPs must understand the risk of severe hypocalcemia in patients with advanced CKD.

Key Risk Message 2: HCPs must understand the need to assess for presence of CKD-MBD before initiating Prolia.

Key Risk Message 3: HCPs must understand the requirement to provide each Prolia patient with a copy of the Patient Guide.

Exposure Variable(s)
N/A

Other Covariate(s)
N/A

Study Sample Size

The goal for the Wave 1 HCP KAB Survey is a sample of at least 371 completed surveys. The survey enrollment window will remain open for the planned duration of the survey even if the target sample of 371 completed surveys is reached. Recruitment may exceed the minimum target sample size since the recruitment window will continue until the pre-specified survey end date, with a data cut-off no sooner than 60 days prior to submission of REMS assessments to the FDA.

Stratified random sampling will be used to select a list of potential respondents. The random sampling process will be performed by a random number generator and considering the ratios of what it is to be stratified by includes medical specialty and geographic location using Statistical Analysis System (SAS®) (version 9.4 or higher). If other demographics of interest are available upon receipt of the recruitment file, they may be considered. This sampling approach will ensure that every HCP eligible for

survey participation has a known probability of selection into the sample and should ensure that the sample is demographically similar to the general population of identified HCPs. Once stratified random sampling is complete, the list will be broken down into batches with 3,000 to be included in each Batch resulting in a total of 3 Batches of 3,000, and Batch 4 to include 1,500 HCPs. The first Batch of 3,000 HCPs will be distributed (further batches may be utilized based on survey uptake).

Additionally, in an effort to ensure that the target sample is proportionately representative of prescribers and non-prescribers, a soft quota will be set to obtain at least 186 completed surveys from prescribers and 185 completed surveys from non-prescribers.

It is important to note that recruitment efforts based on type of prescriber (ie, prescribers and non-prescribers) will be secondary to achieving the overall target sample of completed surveys.

If the HCP KAB Survey sample size for Wave 1 is not achieved, the following measures will be considered to increase HCP response for future waves:

- Increase survey field time to allow HCPs additional time for survey completion.
- Evaluate alternatives to gaining HCP participation (eg, pre-registration).
- Increase compensation.

Data Analysis

Statistical analyses will be primarily descriptive in nature. Counts and percentages will be calculated for each question/item in the questionnaire. Ninety-five percent (95%) CIs for the survey end points will be calculated to provide an estimate of precision; however no formal hypothesis will be tested. All CIs around the percentages will be exact binomial 2-sided 95% CIs calculated according to the method of Clopper-Pearson (Clopper and Pearson, 1934). Analyses will be performed at the respondent level; therefore, within-respondent variation is not relevant.

5. Amendments and Updates

None

6. Rationale and Background

The Prolia® (denosumab) Risk Evaluation and Mitigation Strategy (REMS) was originally approved on 01 June 2010, and the most recent REMS modification was approved on 19 January 2024. Further, the Food and Drug Administration (FDA) accepted

Amgen Inc.'s (hereafter referred to as Amgen) proposed REMS, submitted on 02 February 2024, and formally approved it on 05 March 2024. The modified REMS consists of a communication plan and a timetable for submission of assessments of the REMS. In accordance with section 505-1 of Food, Drug, and Cosmetic Act (FDCA), the FDA determined that a REMS is necessary for Prolia to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD) and chronic kidney disease-mineral bone disorder (CKD-MBD) and to educate healthcare providers (HCPs) regarding:

a) The need to assess for presence of CKD-MBD before initiating Prolia.
b) Their understanding of the requirement to provide each Prolia patient with a copy of the Patient Guide.

The specific objectives to be achieved by the Prolia REMS include:

a) Assess knowledge of the risk of severe hypocalcemia in patients with advanced CKD (estimated glomerular filtration rate [eGFR]CCI
b) Assess knowledge of the need to assess for presence of CKD-MBD before initiating Prolia
c) Assess knowledge of HCP understanding of the requirement to provide each Prolia patient with a copy of the Patient Guide

A component of the Prolia REMS Assessment Plan is the conduct of a quantitative evaluation survey with HCPs identified via Amgen's database, who are currently prescribing and who have the potential to prescribe Prolia, who are part of the REMS Communication Plan outreach, and who have not been debarred or sanctioned in order to assess awareness of the REMS materials, to assess knowledge of the risks associated with Prolia, and to assess knowledge of the requirements of the Prolia REMS.

Findings from the HCP Knowledge, Attitudes, and Behavior (KAB) Survey, together with other REMS evaluation metrics, will be used to assess the Prolia REMS and determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the intended goal.

6.1 Diseases and Therapeutic Area

Prolia is a fully human immunoglobin G2 (IgG2) monoclonal antibody with affinity (equilibrium dissociation constant = 3x x10 12 M) and specificity for human receptor activator of nuclear factor-Kappa B (RANK) ligand (RANKL). Prolia has an approximate

molecular weight of 147 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells. RANKL exists as a transmembrane or soluble protein.

RANKL is essential for the formation, function, and survival of osteoclasts, the sole somatic cell type responsible for bone resorption. Prolia binds to RANKL, preventing RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors.

Prolia is currently indicated in the United States (US) for:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures.
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients, Prolia also reduced the incidence of vertebral fractures.
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.
- Treatment of glucocorticoid-induced osteoporosis in men and women at high risk of fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.

6.2 Rationale

In accordance with Section 505 (1)(f)(3)(A) of the FDCA, the FDA determined that a REMS is necessary for Prolia to ensure the benefits of the drug outweigh the potential risk of CKD.

A component of the Prolia REMS Assessment Plan is the conduct of a quantitative evaluation survey with HCPs identified via Amgen's database, who are current prescribers and those who have the potential to prescribe Prolia, who are part of the REMS Communication Plan outreach, and who have not been debarred or sanctioned in order to assess awareness of the REMS materials, knowledge of the risks associated with Prolia, and knowledge of the requirements of the Prolia REMS.

Findings from the HCP KAB Survey, together with other REMS evaluation metrics, will be used to assess the Prolia REMS and determine whether changes need to be made to

the REMS processes or educational materials to make them more effective in achieving the intended goal.

This combined protocol/statistical analysis plan provides the procedures to be followed with HCPs identified via Amgen's database, who are known to be prescribing Prolia, who are part of the REMS Communication Plan outreach, and who have not been debarred or sanctioned, for inclusion in the 18-month, 3-year, and 7-year Prolia REMS Assessment Reports. This noninterventional study is part of the Prolia REMS Assessment and is a commitment to the FDA.

6.3 Feasibility and Futility Considerations

To effectively evaluate the HCP KAB Survey, Qualitative Research (QR) was conducted on a subset of questions from the draft Wave 1 HCP KAB Survey. QR was conducted with a general population of HCPs who are treating osteoporosis patients.

6.4 Statistical Inference (Estimation or Hypothesis[es])

Statistical analyses will be primarily descriptive in nature. Counts and percentages will be calculated for each question/item in the questionnaire. Ninety-five percent (95%) Confidence Intervals (CIs) for the survey end points will be calculated to provide an estimate of precision; however no formal hypothesis will be tested. All CIs around the percentages will be exact binomial 2-sided 95% CIs calculated according to the method of Clopper-Pearson. Analyses will be performed at the respondent level; therefore, within-respondent variation is not relevant.

7. Research Question and Objectives

The questions and statements in the survey address the goal and objectives of the Prolia REMS and specified key risk messages and are written in several formats, which include:

- Questions or statements with a defined list of possible answers from which the respondent is required to choose one answer (ie, multiple-choice).
- Questions or statements with a defined list of possible answers from which the respondent is required to choose 1 or more answers (ie, Select all that apply).
- Questions or statements with response options of "yes" or "true," or "false," and "I don't know" that require the respondent to indicate agreement or disagreement.

All answers for questions or statements will be tallied to provide a broad picture of the respondent's knowledge, attitudes, and behavior.

The desired response for key risk messages is generally "true" or "yes," indicating knowledge of the objectives of the REMS. However, some questions are formatted to

have the respondent disagree with the statement as written ("false") to avoid having the same affirmative answer for all desired responses.

7.1 Primary

The objectives of the HCP KAB survey are to conduct a survey with HCPs identified via Amgen's database, who are known to be prescribing Prolia, who are part of the REMS Communication Plan outreach, and who have not been debarred or sanctioned in order to assess their awareness and understanding of the risks of Prolia, the Prolia REMS requirements, and the REMS goals and materials:

- Key Risk Message 1: HCPs must understand the risk of severe hypocalcemia in patients with advanced CKD.
- Key Risk Message 2: HCPs must understand the need to assess for presence of CKD-MBD before initiating Prolia.
- Key Risk Message 3: HCPs must understand the requirement to provide each Prolia patient with a copy of the Patient Guide.

7.2 Secondary

N/A

7.3 Exploratory

N/A

8. Research Methods

This is a US-based, observational, cross-sectional survey of HCPs identified via Amgen's database, who are known to be prescribing Prolia, who are part of the REMS Communication Plan outreach, and who have not been debarred or sanctioned. The survey can be self-administered by the respondents via secure internet and telephone modalities utilizing a validated UBC Knowledge Survey System for data collection that is secure for receiving and storing survey data.

All assessments described in this protocol are performed as part of normal clinical practice or standard practice guidelines for the HCP specialty in the US.

Comprehension Pre-Testing of the Survey (Qualitative Research)

To effectively evaluate the HCP KAB Survey, QR was conducted on questions associated with the key risk messages from the draft Wave 1 HCP KAB Survey. QR was conducted with a general population targeting 12 HCPs who are treating osteoporosis patients. The conduct of QR occurred through 1:1 interviews with an experienced Moderator. HCPs who are licensed and/or practicing in Massachusetts,

Minnesota, Vermont, or New Jersey, and who were not debarred or otherwise sanctioned in any US state were not included as part of the QR.

The purpose of QR of select survey questions was to identify potential terms, questions, or topics for clarification or revision based on respondent feedback. Furthermore, the research assessed comprehension among HCP participants regarding the words and phrases used in select survey questions and response options.

QR was carried out in a double-blinded manner. Therefore, during QR respondents did not know the identity of Amgen and the product under study and Amgen did not know the respondents who participate in the study. Following completion of QR and those who opted to receive payment, based on the requirements for reporting payments to the Centers for Medicare & Medicaid Services reporting requirements (otherwise known as the "Sunshine Act") (Patient Protection and Affordable Care Act, 2010), (hereinafter referred to as the "Sunshine Act"), Amgen was provided with information of HCPs who participated in this research for reporting purposes.

HCPs who chose to participate in this research had the opportunity to be compensated. Compensation was made based on medical degree.

Feedback elicited from the QR interviews was used to support the identification of terms, questions, or topics that require clarification or revision, based on areas of confusion or miscomprehension by interviewed participants.

Findings and recommendations from QR were reviewed and incorporated as appropriate to update the select survey questions and response options that were tested, prior to the implementation of the Wave 1 Prolia HCP KAB Survey. A copy of the Final Summary Report titled: Qualitative Research to Evaluate Healthcare Provider Knowledge, Attitudes, and Behavior (KAB) Surveys for Prolia along with the QR moderator discussion guide used to conduct QR, redacted interview transcripts, and the findings presentation is included in ANNEX 5 for final submission of this document to the FDA (See Table 1. for an estimated submission date).

More information regarding QR can be found in the final Plan and Screener located in ANNEX 2.

8.1 Study Design

8.2 Setting and Study Population

The HCP KAB Survey will be administered via the internet or telephone and participants will be able to choose the method that is preferred. The UBC Knowledge Survey System

will be used for both methods of survey administration which has been validated and is secure for receiving and storing survey data. Details on data management are available in Section 8.6.

The projected timeline for program development, survey launch, recruitment, and reporting for Wave 1 is shown in Table 1 below.

Table 1. Projected Timeline for Wave 1 KAB Activities

Milestones	Planned Date[1]
Final Protocol and Survey for QR	CCI
QR	
Protocol and Survey Revision Post QR	
Protocol and Survey Submission to FDA – 90-day review	
UBC Knowledge Survey System Build	
Distribution of Pre-Notification Letter	
UBC Knowledge Survey System in Production (Survey Launch)	
Start of Data Collection Period	
Distribution of Initial Survey Invitation	
First Reminder Mailing (alternating modalities as applicable)	
Second Reminder Mailing (alternating modalities as applicable)	
Outbound Calling to Non-Responders	Not Available[5]
Third Reminder Mailing (alternating modalities as applicable)	CCI
Fourth Reminder Mailing (alternating modalities as applicable)	
End of Data Collection	
Data Processing and Report Development	
Final Wave 1 Assessment Report to FDA	

FDA = Food and Drug Administration; QR = Qualitative Research; UBC = United BioSource LLC
[1] Dates are participant to change based on receipt of FDA comments.
[2] UBC Knowledge Survey System build is being completed in parallel to the FDA review of the HCP Protocol and Survey.
[3] ~16-week survey data collection period.
[4] Approval of the Prolia REMS was on 05 March 2024. Eighteen months post approval is 05 September 2025.
[5] At this time outbound calling is not planned, because the recruitment file does not currently include telephone numbers for each individual HCP.
Note: The dates for Invitation and Reminder Letter processing are approximate and may change based on survey uptake. Additionally, at this time only US Mail is planned, because the recruitment file does not currently include e-mail addresses or fax numbers.

8.2.1 Study Period

Data from the HCP KAB Survey, together with other REMS evaluation metrics, will be used to assess the REMS and determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the goals of the Prolia REMS. The results of the HCP KAB Survey will be included in the 18-month assessment and will continue at Year 3 and Year 7 as required by the FDA.

8.2.2 Selection and Number of Sites

N/A

8.2.3 Healthcare Professional Eligibility

The HCP KAB Survey is planned to be initiated in March 2025 in the US among HCPs identified via Amgen's database, who are currently prescribing and those who have the potential to prescribe Prolia, who are part of the REMS Communication Plan outreach, and who have not been debarred or sanctioned.

Termination of the respondent's participation in the survey will occur if they do not meet the eligibility criteria below.

8.2.3.1 Inclusion Criteria

HCPs must meet all of the following inclusion criteria to be eligible for inclusion in the study:

- HCPs who are currently prescribing and those who have the potential to prescribe Prolia.
- Who are part of the REMS Communication Plan outreach.
- HCPs who have not been debarred or otherwise sanctioned.
- HCPs who have participated in QR.[2]

8.2.3.2 Exclusion Criteria

HCPs meeting any of the following criteria will not be included in the study:

- Respondents who do not agree to participate in the survey. *HCPs who respond 'no' to Question 1 that asks, "Do you agree to participate in this study about Prolia?*".
- Respondents who are currently working for and/or whose immediate family members are currently working for or as a consultant to Amgen, UBC, or the FDA.

[2] Because the target population includes general HCPs, not necessarily those prescribing Prolia, and because of the time in which this qualitative evaluation takes place compared to when the quantitative survey is conducted, allowing those who participated in QR to also participate in the quantitative survey creates no inherent risk in influencing the outcome of whether or not the Prolia HCPs are aware of the REMS objectives.

- Respondents who reported having a conflict of interest.

Further details associated with respondents who do not meet the eligibility criteria established above will be addressed in the assessment report.

8.2.4 Matching - Comparison of the Survey Population to the Prolia REMS Population Analysis

To assess the representativeness of the survey respondents, the survey completers will be compared to the Prolia REMS Population (excluding the survey completers). For this comparison, the Prolia REMS HCP data from the survey completers will be compared to the Prolia REMS HCP population using Chi-square tests; Fisher's exact test will be used if 20% or more of the expected cell counts in the table are less than 5. The following characteristics will be compared: medical specialty and geographic location.

8.2.5 Baseline Period

Given that the survey questions can change over time, there is no specific baseline period for this type of study.

8.2.6 Study Follow-up

N/A

8.3 Variables

8.3.1 Exposure Assessment

N/A

8.3.2 Outcome Assessment

The survey will assess each participant's KAB of the important information as presented in the key risk messages communicated through the Prolia REMS.

The key risk messages, which will be evaluated in this KAB survey, include the following:

- Key Risk Message 1: HCPs must understand the risk of severe hypocalcemia in patients with advanced CKD.
- Key Risk Message 2: HCPs must understand the need to assess for presence of CKD-MBD before initiating Prolia.
- Key Risk Message 3: HCPs must understand the requirement to provide each Prolia patient with a copy of the Patient Guide.
- Survey questions will be pre-tested via QR prior to submission for FDA review as noted in Table 1 above. The key risk message questions can be found in Table 2, Table 3., and Table 4. below.

Table 2. Key Risk Message 1

HCPs must understand the risk of severe hypocalcemia in patients with advanced CKD.		
Question Number	**Questions**	**Desired Response**
7	Are you aware that Prolia is contraindicated in patients with hypocalcemia?	**Yes**
8	Patients with advanced CKD (eGFR CCI [redacted] including dialysis-dependent patients are at greater risk of severe hypocalcemia following Prolia administration.	**True**
11	The presence of CKD-MBD markedly increases the risk of hypocalcemia.	**True**
12	Please select the best answer to complete the sentence. Patients with advanced CKD (eGFR CCI [redacted], including dialysis-dependent patients, are at greater risk of _____.	**severe hypocalcemia following Prolia administration**
16	Pre-existing hypocalcemia is not required to be corrected prior to initiating therapy with Prolia.	**False**

CKD = chronic kidney disorder, CKD-MBD = chronic kidney disorder-mineral bone disease;
eGFR = To achieve the established knowledge threshold of at least 80%, 4 of the 5 questions need to be answered correctly.

Table 3. Key Risk Message 2

HCPs must understand the need to assess for presence of CKD-MBD before initiating Prolia.		
Question Number	**Questions**	**Desired Response**
9	Please select Yes, No, or I don't know for each item. Prior to initiating Prior to initiating Prolia in patients with advanced CKD (eGFR CCI [redacted] including dialysis-dependent patients, evaluate for the presence of CKD-MBD.	
A	CKD-MBD	**Yes**
17	According to the REMS Letter for Healthcare Providers, to minimize the risk of hypocalcemia in patients with advanced CKD, (eGFR CCI [redacted], including dialysis-dependent patients evaluate for the presence of CKD-MBD with iPTH, serum calcium, 25(OH) vitamin D, and 1,25 $(OH)_2$, vitamin D prior to decisions regarding Prolia treatment.	**True**
18	According to the REMS Letter for Healthcare Providers, to minimize the risk of hypocalcemia in patients with advanced CKD (eGFR CCI [redacted] including dialysis-dependent patients you should consider assessing bone turnover status (ie, serum markers of bone turnover or bone biopsy) to evaluate the underlying bone disease that may present.	**True**
19	According to the REMS Letter for Healthcare Providers, you should coordinate care with HCPs who have expertise in CKD-MBD for patients with advanced CKD.	**True**

HCPs must understand the need to assess for presence of CKD-MBD before initiating Prolia.		
20	Please fill in the blank by selecting one option from the list below. According to the REMS Letter for Healthcare Providers, to minimize the risk of hypocalcemia in patients with advanced chronic CKD, monitor the patients' serum calcium weekly for _____?	**weekly for first month after Prolia administration and monthly thereafter**

To achieve the established knowledge threshold of at least 80%, 4 of the 5 questions need to be answered correctly.

Table 4. Key Risk Message 3

HCPs must understand the requirement to provide each Prolia patient with a copy of the Patient Guide.		
Question Number	**Questions**	**Desired Response**
13	Please select the correct answer to the following statement. According to the REMS Letter for Healthcare Providers, patients should be provided with a copy of the:	**Patient Guide**
14	According to the REMS Letter for Healthcare Providers, you are required to review the Patient Guide with each patient, including the serious risk of Prolia and the symptoms of severe hypocalcemia.	**True**
15	According to the REMS Letter for Healthcare Providers, all Prolia patients should be advised to seek prompt medical attention if they have signs or symptoms of severe hypocalcemia.	**True**

To achieve the established knowledge threshold of at least 80%, all 3 questions need to be answered correctly.

The HCP KAB Survey will also collect demographic characteristics for HCPs who complete all survey questions.

These include:

- Medical degree of respondent
  - Medical Doctor (MD), Doctor of Osteopathy (DO), Physician Assistant (PA), Advanced Practice Registered Nurse (APRN), including Certified Nurse Practitioner (CNP), Clinical Nurse Specialist (CNS).
- Medical Specialty
- Number of years practicing as an HCP
- Prescriber versus Non-Prescriber
- Past Completer versus Current Completer (beginning with Wave 2)
- Geographic location

Eligibility and reasons for ineligibility will be presented by counts and percentages.

8.3.3 Covariate Assessment

N/A

8.3.4 Validity and Reliability

N/A

8.4 Data Sources

The survey will be administered via a secure web-based internet connection, which will allow respondents who choose to participate to do so at a time and location that is convenient for them. The survey is written to reflect wording for both methods of survey administration: internet and telephone.

The structured survey comprises questions or statements written in several formats, which include specific key risk messages:

- Questions or statements with a defined list of possible answers from which the respondent is required to choose one answer (ie, multiple-choice).
- Questions or statements with a defined list of possible answers from which the respondent is required to choose one or more answers (eg, Select all that apply).
- Questions or statements with response options of “yes” or “true,” “no” or “false,” and “I don’t know” that require the respondent to indicate agreement or disagreement.

All answers for questions permitting multiple responses will be combined as part of the cumulative total to provide a broad picture of HCPs’ knowledge, attitudes, and behavior.

The desired response for key risk messages is generally “true” or “yes” indicating knowledge of the objectives of the Prolia REMS. However, some questions are formatted to have the respondent disagree with the statement as written (“false” or “no”) to avoid having the same affirmative answer for all desired responses. Whenever possible within a key risk message, there will be an equal balance of questions with a “true” or “yes” and “false” or “no.”

Information via Amgen’s database will identify HCPs who are currently prescribing and those who have the potential to prescribe Prolia, who are part of the REMS Communication Plan outreach, and who have not been debarred or sanctioned. The total number as of April 2024 is approximately 10,500 HCPs. Given that the total number of HCPs is broad, the list will be stratified by medical specialty and geographic location and randomized and divided into 4 Batches, Batches 1-3 will include 3,000 HCPs and Batch 4 will include the remaining 1,500 HCPs. Batch 1 will be utilized to distribute the initial invitation at survey launch and depending upon survey uptake, subsequent batches may be deployed, potentially resulting in all HCPs being invited to participate in the survey.

The HCP characteristics captured in this dataset include medical specialty, National Provider Identifier (NPI) number, state medical license number, state of practice, facility first name, last name, and mailing address. Any additional contact information (ie, e-mail/phone/fax) may be retrieved from an external source closer to survey launch.

8.5 Study Size

Wave 1 will aim to reach, at a minimum, CCI [redacted] for HCPs. Each survey wave will remain open for the entire scheduled fielding time but will close no earlier than 60 days prior to assessment report submission.

Personalized invitations will be sent to each selected participant using electronic outreach and/or US Mail for communication Table 1.

In an effort to ensure maximum participation in the survey, all potential participants identified at a designated interval prior to survey launch will receive a Pre-Notification Letter explaining the purpose and details of the upcoming survey. The Pre-Notification Letter will identify the method available for survey completion: internet or telephone. This letter will be targeted for distribution approximately 2 weeks prior to survey launch.

After the Pre-Notification Letter has been sent, upon launch of the survey, the first Batch of 3,000 HCPs will be sent an Invitation Letter. *Remaining batches may be distributed based on survey uptake.

The Invitation Letter will include:

- Two methods (internet or telephone) for accessing the survey: a Quick Response Code (QR code) for quick access, via a mobile device, to the secure website and a Uniform Resource Locator (URL) for the internet survey and a toll-free number to the Survey Coordinating Center (SCC) for the telephone interview.
- A unique code that the respondent must provide when accessing the survey via the internet or telephone.
- Notification that the survey should take approximately 25 minutes to complete depending on method chosen to complete it.
- Notification that payment meeting a fair market value amount will be provided to thank them for their participation, if eligible and or elect to receive the compensation.
- Notification that participation in the survey will not affect their ability to prescribe Prolia.
- Notification that eligible participants will receive compensation (if the respondent is able or chooses to receive compensation) for completing the survey. Additionally, potential participants who are not eligible for compensation will be informed that, while they will not receive compensation for their participation, they may still participate in the survey but will not be compensated.

All HCPs who do not respond to the survey, regardless of the response rate, will be sent Reminder Letters that will assist in informing non-responders that others have completed the survey and letting them know that their help is needed to encourage them to respond to the survey (social validation). The intervals for sending Reminder Letters to non-responders will be condensed as necessary based on the actual rate of survey accrual relative to the proximity of the target survey close date and no sooner than 60 days prior to submission of the 18-month REMS assessment report to the FDA. Reminder letters will be flagged with terms associated with social validation, for example, Reminder 1 - "Friendly Reminder," Reminder 2 - "We need your help," Reminder 3 – "Please Respond," and Reminder 4 - "Final Reminder" will be implemented. Stratified random sampling will be used to select a list of potential respondents (Section 8.9.1.3). Furthermore, in order to minimize sampling error and bias, at least 3 but potentially 4 Reminder Letters will be issued (Table 1). Note that at this time e-mail addresses, telephone numbers, and fax numbers are not available. It is possible that closer to survey launch this information may be obtained to help to reduce coverage bias. If telephone numbers are acquired and outbound calling is needed, it will occur.

Depending on available contact information, returned letters may be evaluated for redistribution using an alternate mode of delivery to the respondent.

8.6 Data Management

A secure, web-based, proprietary Knowledge Survey System designed and built by UBC will be used for the HCP KAB Survey. The system meets Title 21 Code of Federal Regulations (CFR) Part 11, the Health Insurance Portability and Accountability Act (HIPAA) and the California Consumer Privacy Act guidelines for information systems. Respondent-identifying information will be stored separately from the survey responses.

Title 21 CFR Part 11 applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any records requirements set forth in Agency regulations; the application must provide protection, security, and dependability. Protection of the data requires that audit trails be under application control for all updates and deletions, and that date and time stamps are available. The UBC Knowledge Survey System maintains an audit trail containing date and time stamps.

The security of the application requires physical and logical security. The UBC Knowledge Survey System maintains user and group-level permissions, so that only relevant project team members will have appropriate access to the system.

Dependability of the application requires that the database be validated and documented evidence that the application does what it is purported to do and will continue to do so. UBC will thoroughly validate and document the testing of the UBC Knowledge Survey System. The validation of this system begins with the development of a Project Strategy Document. The document details the strategy for testing. Product Backlog Items are created, and test scripts are written and executed.

All associated Title 21 CFR Part 11 requirements, including requirements for data entry, audit trails, date and time stamps, and security, are tested at baseline.

When survey respondents access the survey website to complete an online survey, they will be asked to enter the unique code from the invitation letter and pass the CAPTCHA (Completely Automated Public Turing test to tell Computers and Humans Apart) robot check shown on the screen. After the respondent has correctly entered the code and passed the CAPTCHA test, the system will advance to the survey welcome page from which the respondent can access the actual survey.

After the UBC end users, who can facilitate completion of a survey with a respondent via telephone, access the survey website for entry of survey information collected from respondents over the telephone, they will click “UBC Login” and enter their UBC network credentials. They will then access the survey assigned to the respondent by matching the code provided to the respondent code in the system.

All data entered will be single data entered by either the respondent or a designated UBC resource who has been trained to enter data for this program. Data will be checked in real time to ensure it is being entered according to acceptable parameters and requirements. This process will include a data extract, at a time point during survey execution where the data collected is a reasonable number (ie, more than 50 completed surveys). This data extract will then follow the process in which it will be mapped to Statistical Analysis System (SAS®) datasets and evaluated for any parameters that were not planned (ie, skip pattern errors).

At the end of each survey cycle, the same process as outlined above will be followed which includes having all data extracted from the UBC Knowledge Survey System and

mapped to SAS datasets (SAS V9.4 or higher). The mapping of raw data will be validated, as will the programming of the analysis tables created from the SAS datasets.

8.6.1 Data Collection Tools (DCTs)/Electronic Data Record

As used in this protocol, the term data collection tool (DCT) (the survey) should be understood to refer to an electronic data record.

A completed DCT (the survey) is required for each included respondent. As defined (Section 8.7.1), a Completed Survey (Primary Population) is the population for the majority of the analyses includes only those respondents who completed all eligibility questions, met all inclusion criteria and none of the exclusion criteria, and answered all questions associated with at least 1 key risk message. The completed original DCTs (the surveys) are the sole property of Amgen and should not be made available in any form to third parties, except for authorized representatives of Amgen or appropriate regulatory authorities, without written permission from Amgen. UBC shall ensure that the DCTs (the surveys) are securely stored at UBC on a secure server to prevent access by unauthorized third parties.

UBC has ultimate responsibility for the collection and reporting of all data entered on the DCTs (the surveys) as required and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The DCT (the survey) serves as the source document. Any corrections to entries made in the DCTs (the surveys) must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

8.6.2 Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Amgen, UBC agrees to keep all study-related records. The records should be retained by UBC according to local regulations or as specified in the Fully Executed Statement of Work, whichever is longer. UBC must ensure that the records continue to be stored securely for so long as they are retained.

If UBC becomes unable for any reason to continue to retain study records for the required period, Amgen should be prospectively notified. The study records must be transferred to a designee acceptable to Amgen.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless UBC and Amgen have expressly agreed to a

different period of retention via a separate written agreement. Record must be retained for longer than 15 years if required by applicable local regulations.

UBC must obtain Amgen's written permission before disposing of any records, even if retention requirements have been met.

8.6.3 Obtaining Data Files

N/A

8.6.4 Linking Data Files

N/A

8.6.5 Review and Verification of Data Quality

N/A

8.7 Data Analysis

8.7.1 Analysis Populations

Data from all respondents who access the survey will be collected. Only data from those survey respondents who were eligible to participate in the survey and answered every question ("completers") will be the primary analysis population. The population included in the analysis will be defined as follows:

- All Respondents – The "All Respondents" population consists of respondents who accessed the survey using a unique code. This population will be used as the denominator for percentages in survey administration statistics and in the survey eligibility results analysis. This population includes any individual who accesses the survey, regardless of whether or not they meet the study's eligibility criteria.
- Eligible Respondents – The "Eligible Respondents" are those who completed all eligibility questions designated as eligible for the survey, regardless of whether or not they completed the entire survey.
- Non-Completed Surveys – The population will be considered "Non-Completers" if the respondent completed all eligibility questions and answered at least 1 question associated with one key risk message but did not complete the entire survey.
- Completed Surveys (Primary Population) – The population for the majority of the analyses includes only those respondents with completed surveys. "Completed" is defined as an eligible respondent who completed all eligibility questions, met all inclusion criteria and none of the exclusion criteria, and answered all questions associated with at least 1 key risk message. Any remaining questions not answered by this population will be identified in each analysis as either "missing data" if the respondent discontinued the survey before answering the question(s) or skipped the question, or "N/A" if the question(s) was not presented to the respondent due to skip logic in the survey. The "completed surveys" population will be a subset of the "eligible respondents" population.

8.7.2 Planned Analyses

Statistical analyses will be descriptive in nature. Counts and percentages will be calculated for each question/item in the questionnaire. Ninety-five percent (95%) CIs for the survey end points will be calculated to provide an estimate of precision; however no formal hypothesis will be tested. All CIs around the percentages will be exact binomial 2-sided 95% CIs calculated according to the method of Clopper-Pearson. Analyses will be performed at the respondent level; therefore, within-respondent variation is not relevant.

8.7.3 Survey Administration Analyses

The survey administration data to be described in the HCP KAB assessment report includes:

- Number of Pre-Notification Letters distributed
- Number of Pre-Notification Letters returned as undeliverable
- Number of Invitation Letters distributed
- Number of Invitation Letters returned as undeliverable
- Number of Reminder Letters distributed
- Number of Reminder Letters returned as undeliverable
- Response rate after the Invitation Letter
- Response rate after each Reminder Letter
- Number of respondents screened for participation (All respondents)
- Number of respondents eligible for participation
- Number of respondents not eligible for participation
- Number of respondents eligible for participation who completed the survey
- Number of respondents who completed the survey via internet or telephone
- Time to complete survey (minutes)
- Description of survey participants includes:
  - Type of HCP (MD, DO, APRN*, PA, Other)
    - *Includes CNP and CNS
  - Medical Specialty
  - Length of time working as an HCP
  - Length of time prescribing Prolia
  - Geographic region
  - Survey completion status

Eligibility and reasons for ineligibility will be presented by counts and percentages.

8.7.3.1 Primary Analysis

The primary analysis for each wave will be executed upon data lock and data extraction of the KAB Survey.

8.7.4 Planned Method of Analysis

8.7.5 General Considerations

Statistical analyses will be primarily descriptive in nature, with 95% CIs (inferential statistics) for primary and secondary endpoints to generalize the results to the entire targeted population; however, no formal hypothesis will be tested. All analyses will be performed at the respondent level; therefore, within-respondent variation is not relevant. In the case where the estimated percentage is equal to zero or 100 percent, the Clopper-Pearson method (Clopper and Pearson, 1934) will be utilized to estimate the CIs for zero and 100% using procedure freq in SAS (Nair, 2014). The following SAS code is provided below.

```
Proc freq data=<data>;
by <variable>;
tables <variable> / binomial (level = x) alpha = 0.05;
weight count /zero;
```

CIs for primary and secondary end points will be calculated as inferential statistics to generalize the results to the entire targeted population. The p-values for comparison of how representative the respective survey respondents are to the respective stakeholder population will be obtained from the Chi-square test.

A prespecified threshold of at least 80% has been set. This prespecified threshold aligns with the FDA general guidance that 80% or higher should be the general standard for each REMS key risk message.

Example Table Output 1: Secondary Analysis of Key Risk Message 1 - Completed Surveys

Correct Responses	Overall (N=XX)[a] n (%) [95% CI][b]
0 correct responses	XX (XX.0)
1 correct response	XX (XX.0)
2 correct responses	XX (XX.0)
3 correct responses	XX (XX.0)
4 correct responses	XX (XX.0)
Demonstrated understanding of Key Risk Message 1[c]	XX (XX.0) [XX.X - XX.X]

[a] Total number of eligible respondents completing the survey.
[b] 95% exact 2-sided CIs are calculated using the Clopper-Pearson method.
[c] To demonstrate understanding of Key Risk Message 1, the respondent must have answered 4 of the 4 questions correctly.

8.7.6 Primary Analysis

Primary analyses are performed for all key risk message questions and will be stratified by prescriber versus non-prescriber. Responses from all questions/items from each key risk message will be summarized by counts and percentages. The primary analysis for a key risk message evaluates the rate for each correct response to each individual question/item defined by the key risk message. "Select all that apply" questions will be counted as a single correct response if the respondent selects 80% or more of the correct responses and does not select any incorrect response. The specific correct response to each question/item is identified in the body of the Key Risk Message Table 2, Table 3., and Table 4.. Exact binomial two-sided 95% CIs will be calculated for the proportion of respondents who provide the correct responses. The completed surveys (Primary Population) will be used for this analysis.

8.7.7 Secondary Analysis

The secondary analysis of the key risk messages will be stratified by prescriber versus non-prescriber and will be performed consisting of a frequency distribution of the number of correct responses to each key risk message (ie, number and percentages will be shown by the number of correct responses). "Select all that apply" questions are handled as described in Section 8.7.6. Only those items that are presented to all respondents will be included in the secondary analysis. The completed surveys (Primary Population) will be used for this analysis.

Example Table Output 2: Primary Analysis of Responses to Questions Linked to Key Risk Message 1 - Completed Surveys

Question	Prescriber	Non-Prescriber	Overall (N=XX)[a] n (%) [95% CI][b]
Question 1:			
Number not missing (if applicable)	XX	XX	XX
Yes[c]	XX (XX.0) [XX.X - XX.X]	XX (XX.0) [XX.X - XX.X]	XX (XX.0) [XX.X - XX.X]
No	XX	XX	XX
I don't know	XX	XX	XX

[a] Total number of eligible respondents completing the survey.
[b] 95% exact 2-sided CIs are calculated using the Clopper-Pearson method.
[c] Correct response.

Another endpoint is the demonstrated understanding of each key risk message, defined as answering 80% or more questions/items in a key risk message correctly. "Select all that apply" questions are handled as described in Section 8.7.6. The proportion of respondents who demonstrated understanding of the key risk message will be presented with 95% CIs. Additionally, the number and percentages of respondents who demonstrated understanding of all key risk messages will be provided with 95% CIs. In this analysis, the proportion of respondents who demonstrated an understanding of the key risk message will be presented with 95% CIs. The REMS will be considered meeting its goals if the point estimates of Key Risk Message 1, Key Risk Message 2, and Key Risk Message 3 receive a demonstrated understanding of 80% or above. Additionally, the number and percentages of respondents who demonstrated understanding of all key risk messages will be provided with 95% CIs. As stated in the FDA draft Guidance for "Survey Methodologies to Assess REMS Goals That Relate to Knowledge: Guidance for Industry" although there is no standard knowledge performance threshold that is generally accepted for all REMS Programs, in most cases it should be 80% or higher for each Key Risk Message. The completed surveys (Primary Population) will be used for this analysis.

8.7.8 Trend Over Time Analysis

A descriptive comparison in correct response rates to Key Risk Message questions and the demonstrated understanding of each Key Risk Message across the survey waves will be conducted to address possible trends in the knowledge rates of the survey completers. For the trend analysis, only those questions will be considered for the demonstrated understanding rates that are asked in all survey waves. Therefore, the

demonstrated understanding rates in the trend analysis may differ from the results of the previous waves. Additionally, the comparison will be completed to include no more than two previous waves and the current reporting period only. If any changes to the questions and/or the response options are made across the survey waves, those questions/responses will be identified as changed with an applicable footnote for identification.

This analysis will be performed following the completion of Wave 2.

8.7.9 Sub-Group Analysis

Subgroup analyses will be performed using the primary population (Completed Surveys) for each key risk message for both the primary and secondary analysis based on descriptive statistics. The sub-group analyses that will be performed will be by medical degree of respondent, medical specialty, number of years practicing as an HCP, number of patients being treated with Prolia, awareness of the educational materials, responder versus non-responder previous completer versus past completer (to be performed beginning with Wave 2), and geographic location.

The denominator for the calculation of percentages is the number of available responses. All sub-group analyses will be programmed; however, only those with a meaningful sample size, ie, 50 or more respondents in at least 2 sub-groups, will be described in the Assessment Report. Sub-groups with low sample size may also be combined as appropriate.

All sub-groups will be derived from the survey data.

8.7.10 Analysis of Additional Survey Questions

All other questions, including those about demographics, inclusion/exclusion, behaviors, safety, requirements of the Prolia REMS and awareness of the REMS educational materials, will be analyzed using descriptive statistics. The responses to each question will be summarized by frequency tables.

8.7.11 Categorization and Verbatim Responses

Free text and verbatim responses will be presented in data listings and, as appropriate, may be categorized for categorical data analysis.

8.7.11.1 Missing, Duplicate, or Incomplete Data and Lost to Follow-up

8.7.12 Missing Data

Regardless of survey method (internet/telephone) chosen to participate, there is a potential for missing data associated with demographic questions and non-related key

risk message questions (the main survey content). Any remaining questions not answered by this population will be identified in each analysis as either "missing data" if the respondent discontinued the survey before answering the question(s) or skipped the question, or not applicable ("N/A") if the question(s) was not presented to the respondent due to skip logic in the survey. The "completed surveys" population will be a subset of the "eligible respondents" population.

8.7.13 Duplicate Data

With any voluntary survey there is a possibility of duplicate surveys being received. If it is discovered that a respondent completed more than 1 survey (eg, during fulfillment reconciliation), only the results from the first completed survey (based on time completed) will be included in the analyses.

8.7.13.1 Descriptive Analysis

8.7.13.1.1 Description of Study Enrollment

The target sample size was derived based on the total population available and calculated per the FDA draft guidance identifying the estimated population including a margin of error of ± 5% and 95% CIs.

Additionally, in an effort to ensure that the target sample is proportionately representative of prescribers and non-prescribers, a soft quota will be set to obtain at least 186 completed surveys from prescribers and 185 completed surveys from non-prescribers.

It is important to note that recruitment efforts based on type of prescriber (ie, prescribers and non-prescribers) will be secondary to achieving the overall target sample of completed surveys.

Table 5. shows the precision of the estimated level of understanding for the key risk messages identified for HCPs with exact binomial 2-sided 95% CIs for a sample size of 371 completed surveys.

CCI

[redacted]

8.7.13.1.2 Description of Participant Characteristics

HCPs who are currently prescribing and those who have the potential to prescribe Prolia, who are part of the REMS Communication Plan outreach, and who have not been debarred or sanctioned will be invited to participate in this survey.

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

Exact binomial 2-sided CIs are used to indicate that for an estimated comprehension level, the true population level of comprehension is at least as high as the lower limit of the 95% CI and may be as high as the upper limit of the 95% CI.

8.7.13.3 Sensitivity Analysis

N/A

8.7.13.3.1 Subgroup Analysis

The planned subgroups include the following:

- Medical degree of respondent (MD, DO, APRN*, PA, Other) *Includes CNP and CNS
- Medical specialty
- Number of years practicing as an HCP
- Number of patients being treated with Prolia
- Awareness of the REMS educational materials (ie, REMS Letter for Healthcare Providers, Patient Guide)
- Previous Completer versus New Completer (to begin with Wave 2)
- Geographic location

8.7.13.3.2 Stratified Analysis

N/A

8.7.13.3.3 Sensitivity Analysis for Residual Confounding and Bias

N/A

8.7.13.3.4 Other Sensitivity Analysis

N/A

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

Safety data will not be collected or analyzed in this study.

8.8 Quality Control

The UBC Knowledge Survey System programming will be reviewed by UBC's Quality Control (QC) and simulated users [User Acceptance Testing (UAT)] prior to implementation. At the completion of data collection, the Knowledge Survey System data will be mapped to SAS datasets (SAS v9.4 or higher) by a SAS programmer/designee. These original SAS datasets will be validated by double programming and QC. The validated original SAS datasets will then be used by a SAS programmer to create a set of summary tables and listings according to the analysis text and mock-up tables. If derived analysis datasets are required to produce these summary tables, the derived analysis datasets will be created and independently validated according to Standard Operating Procedures (SOPs). All TL (Tables and Listings) output will be independently validated and documented according to the established SOPs. Summary tables will be reviewed by the appropriate team members

and included in the assessment report that is sent to Amgen along with the final document to be submitted to the FDA. No respondent contact information is included in the tables or in the assessment report.

8.9 Limitations of the Research Methods

The KAB survey recruitment strategies are intended to recruit HCPs who are currently prescribing and those who have the potential to prescribe Prolia, who are part of the REMS Communication Plan outreach, and who have not been debarred or sanctioned. Participants will be self-selected because they will voluntarily respond to the invitation to participate, so the potential exists that those who choose to respond to the survey may differ in their understanding of the REMS Program from those who elect not to participate. This is a common limitation of all studies that rely on voluntary participation.

The second limitation is that the survey can assess HCPs' understanding of the REMS, but it cannot clearly determine which channel the respondents gained the information from. While the survey asks HCPs where the information was gained, recall of information may not be reliable. Inherent in survey research is the reliance on the respondent's recall of whether or not the REMS educational materials (eg, REMS Letter for Healthcare Providers) were received and read. It is possible, however, that respondents may simply not recall receiving and/or reading any 1 or more of the REMS educational materials that were, in fact, received and/or read. It is also possible that the respondents have acceptable understanding of the important product information associated with the use of Prolia despite not receiving or recalling that s/he received and/or read the REMS educational materials prior to completing the survey.

A third limitation is the inclusion of HCPs who are not actively prescribing Prolia, but rather have the potential to prescribe Prolia. This population of HCPs is critical to ensure that all HCPs (prescribers and non-prescribers) are evaluated equally. However, at the time of data lock it is possible that the data may be constrained based on knowledge associated with the Prolia REMS from those who are non-prescribers. To ensure that the data evaluated is clear, a stratification of prescribers versus non-prescribers will be implemented for both primary and secondary analyses.

A fourth limitation is that of social desirability where respondents are more likely to answer "yes" when they are asked "did you read this?" or "did you do this?" because they assume this is the expected answer. Social desirability bias tends to result in higher scores, particularly for questions with a true/false response.

8.9.1.1 Measurement Error(s)/Misclassification(s)

N/A

8.9.1.2 Information Bias

A number of controls will be in place to ensure the survey is conducted in a professional manner and to minimize biases, including the following:

A standardized script will be used for telephone interviews, and all telephone interviewers will be carefully trained in interview techniques in order to minimize interviewer bias.

The survey will be programmed to ensure:

- Questions are asked in the appropriate sequence and all questions will be presented in a standard order to reduce exposure bias.
- Respondents cannot skip ahead and will only allow for missing data when caused by skip patterns.
- The list of response options within a multi-item question are randomized to minimize the potential for positional bias.

Regardless of the method chosen to complete the survey, respondents will be instructed that they cannot go back to a question once they have progressed to the next question and cannot skip ahead. Both the telephone and the internet questionnaire will be programmed with a standardized approach.

Respondents will be provided with a unique code during the recruitment process and will then be asked to provide the unique code to gain access to the internet-based system or when calling the SCC. The code will be inactivated after use to minimize exposure bias and fraud.

8.9.1.3 Selection Bias

Potential participants will be self-selected since they will voluntarily respond to the invitation to participate. Reminder letters will be sent to non-responders to reduce non-response bias.

Additionally, the following measures are in place to assist in minimizing potential biases in the survey sample:

The population of potential participants are those as defined in Section 8.2.3. Stratified random sampling will be used to select a list of potential respondents. This sampling approach will ensure that every HCP eligible for survey participation has a known probability of selection into the sample and should ensure that the sample is

demographically similar to the general population of identified HCPs (ie, medical specialty and geographic location). The random sampling process will be performed by a random number generator and taking into account the ratios of what it is to be stratified by (ie, medical specialty and geographic location) using SAS® (version 9.4 or higher).

- To reduce exposure bias, the following will be excluded:
  - Respondents who do not agree to participate in the survey.
  - Respondents who are currently working for and/or whose immediate family members are currently working for or are consultants to Amgen, UBC, or the FDA.
  - Respondents who report having a conflict of interest.
- Two methods are available for survey completion: internet and telephone. Providing more than 1 method for survey data collection allows for wide survey access to a heterogeneous population and minimizes intervention bias.
- The list of respondent names will be checked for duplicates so that an individual's responses will not be included in the survey assessment more than once.

8.9.1.4 Confounding

N/A

8.9.2 External Validity of Study Design

N/A

8.9.3 Analysis Limitations

N/A

8.9.4 Limitations Due to Missing Data and/or Incomplete Data

N/A

8.10 Other Aspects

If any protocol deviations occur during survey processing that may have an impact on the survey data and analysis, they will be reported in the final assessment report.

9. Protection of Human Participants

9.1 Informed Consent

The survey will begin with an introduction to the survey providing the respondents with general information about the research sponsor and the survey expectations followed by letting them know how their information will be used, how their privacy will be protected, how they can learn more about the survey, and instructions on taking the survey. Once this information is reviewed and the respondents proceed to the first survey question, they will be presented with one final statement which is: "Your agreement to participate

in this survey confirms mutual understanding in connection with completion of the survey and compensation to be rendered in connection with those services", concluding with their first question asking if they agree to participate in the survey about Prolia. If respondents select "Yes" they will proceed through the screening module to confirm their eligibility and should they select "No", the survey will immediately terminate, and their session will end. If deemed ineligible, respondents participating via the internet-based survey are immediately notified with a "thank you" message that their survey participation has ended. For those respondents participating in the survey via the telephone with the SCC, the SCC Associate will communicate the "thank you" message that, based on the respondent's answer, they are not eligible to participate.

9.2 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

It is the responsibility of UBC to have prospective approval of the study protocol, protocol amendments, materials describing the consent process (eg, statement regarding agreement to participate), and other relevant documents, (eg, recruitment advertisements), if applicable, from the Institutional Review Board (IRB). All correspondence with the IRB should be retained by UBC. Copies of IRB approvals should be forwarded to Amgen.

Please note that IRB approval is not required for this study.

9.3 Participant Confidentiality

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

Participant will be assigned a unique identifier by the sponsor. All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant personal data. Such measures will include omitting participant names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

Participant personal data will be stored at UBC in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. UBC will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, UBC shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Amgen and other authorized parties, any participants names will be removed and will be replaced by a single, specific, numerical code. All other identifiable data transferred to Amgen or other authorized parties will be identified by this single, participant-specific code. UBC will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In the case of data transfer, Amgen will maintain high standards of confidentiality and protection of participants' personal data consistent with the vendor contract and applicable privacy laws.

For serious adverse events (AEs) reported to Amgen, participants are to be identified by their unique participant identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (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.

In compliance with [governmental regulations/ International Council for Harmonisation Good Clinical Practice (ICH GCP) Guidelines], it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the [IRB/IEC] direct access to review the participant's original medical records for verification of 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 participant to permit such individuals to have access to his/her study-related records, including personal information.

9.4 Participants Decision to Withdraw

Participants have the right to withdraw from the study at any time and for any reason.

Withdrawal of consent for a study means that the participant does not wish to or is unable to continue further study participation. Participant data up to withdrawal of consent will be included in the analysis of the study and, where permitted, publicly available data can be included after withdrawal of consent. As per local regulations, upon withdrawal of consent, the participant has the right to request removal of their data that was collected and not have it further processed. The investigator is to discuss with the participant appropriate steps for withdrawal of their consent from the study.

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

10.1 Definition of Reportable Events

10.1.1 Adverse Events

An AE is any untoward medical occurrence in a participant 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)

Adverse Device Effect

An adverse device effect is any adverse event related to the use of a combination product or 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, or adverse events resulting from use error or from intentional misuse of the device.

10.1.2 Serious Adverse Events

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

- is fatal
- is life threatening (places the participant/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 medically important serious event” 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 medically important serious events” refer to important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant/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, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

10.1.3 Other Safety Findings (OSF)

Other Safety Findings (regardless of association with an adverse event) include:

- Medication errors, overdose/underdose, whether accidental or intentional, misuse, addiction, or abuse involving an Amgen product,
- Use of an Amgen product while pregnant and/or breast feeding,
- Transmission of infectious agents,
- Reports of uses outside the terms for authorized use of the product including -off label use,
- Accidental or Occupational exposure,
- Any lack or loss of intended effect of the product(s).

10.1.4 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 drug, combination product, or device after it is released for distribution to market or clinic. This includes any drug(s), device(s) or combination products provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) or combination product(s) includes investigational product.

10.2 Safety Collection, Recording and Submission to Amgen Requirements

This study is collecting information from Healthcare Professionals prospectively at one point in time through the completion of an online-based survey or telephone-based survey. All reportable events (adverse events, product complaints, and other safety findings) considered to have occurred following exposure to Prolia will be collected following Healthcare Professional enrollment within the study through to the final study contact. The Vendor is responsible for ensuring that all reportable events they become aware of during the study period are recorded in the appropriate study documentation. It is the Vendor's responsibility to evaluate whether an adverse event is related to an Amgen product prior to reporting the adverse event to Amgen. If further safety-related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the Vendor/participants. All reportable events must be submitted as individual safety reports to Amgen Safety via the

applicable Amgen Safety Reporting Form (paper or electronic form) within the timelines stated in Table 6 below.

Table 6. Types of Safety Data to be Collected and Reported in primary data collection studies collecting all reportable events

Reportable Events/Event Type	* Reporting Timeframe
• Serious Adverse Events (related and non-related) • Other Safety Events (related and non-related) • Product Complaints (serious and non-serious) • Other Safety Findings (serious and non-serious) • Pregnancy and/or Lactation Exposure	• Within 1 business day from when Vendor first becomes aware of the event
• Non-serious Adverse Events (related and non-related)	• Within 15 calendar days from when Investigator/Vendor first becomes aware of the event

**** Please note, more stringent reporting timelines may apply per local requirements***

Reportable events that are suspected to be related to any Amgen medicinal product, combination product or device where there is no exposure to Prolia should be spontaneously reported to Amgen within 1 business day of vendor's awareness. A list of all Amgen medicinal products can be found in the following link: https://wwwext.amgen.com/amgen-worldwide

To spontaneously report a reportable event to Amgen, refer to the following link to locate your Local Amgen contact information by country: https://wwwext.amgen.com/contact-us/product-inquiries

Additional details on what to collect and report to Amgen for the reportable event can be found in the following link: https://wwwext.amgen.com/products/global-patient-safety/adverse-event-reporting

Reportable events suspected to be related to any non-Amgen medicinal product should be reported to the local authority in line with the local country requirements.

See APPENDIX C for sample Safety Report Form(s) and APPENDIX D for sample Pregnancy and Lactation Notification Forms. The Investigator may be asked to provide additional information for any event submitted. Information provided about the event must be consistent with information recorded in the study documentation where safety data may also be recorded.

10.2.1 Collection of Pregnancy and Lactation Information

Female Patients Who Become Pregnant

The vendor will collect pregnancy information on any female patient who becomes pregnant following exposure to Prolia if reported by the Healthcare Professional during completion of the online-based survey or telephone-based survey.

Information will be recorded on the Pregnancy Notification Form (see Appendix D). The worksheet must be submitted to Amgen Safety within 1 business day of when Vendor first becomes aware of the patient's pregnancy (Note: Vendor is not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).

After receipt of the Pregnancy Notification Form, Amgen Safety will provide the Healthcare Professional with a consent form and questionnaire to collect additional information. After obtaining the female patient's signed consent for release of pregnancy and infant health information, the Healthcare Professional will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female patient who becomes pregnant following exposure to Prolia through 6 months after the last dose of Prolia. This information will be forwarded to Amgen Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

Any termination of pregnancy will be reported to Amgen Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is considered another safety finding, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.

If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female patient experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the Vendor will report the event as a serious adverse event.

Male Patients with Partners who Become Pregnant or Were Pregnant at the Time of Enrollment

In the event the Healthcare Professional notifies the vendor of a male patient who fathers a child following exposure to Prolia, the information will be recorded on the Pregnancy Notification Form. The form (see Appendix E) must be submitted to Amgen Safety within 1 business day of when the Vendor first becomes aware of the pregnancy. (Note: Vendor is not required to provide any information on the Pregnancy Notification Form that violates the country or region's local privacy laws).

After receipt of the Pregnancy Notification Form, Amgen Safety will provide the Healthcare Professional with a consent form and questionnaire to collect additional information. The Healthcare Professional will attempt to obtain a signed consent for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.

After obtaining the female partner's signed consent for release of pregnancy and infant health information, the Healthcare Professional will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Safety.

Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

Any termination of the pregnancy will be reported to Amgen Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

Vendor will collect lactation information on any female patient who breastfeeds while taking Prolia through 6 months after last dose if reported by the healthcare professional during completion of the online-based survey or telephone-based survey.

Information will be recorded on the Lactation Notification Form (see Appendix D) and submitted to Amgen Safety within 1 business day of when the Vendor's first becomes aware of the lactation exposure.

With the female patient's signed consent for release of mother and infant health information, the Healthcare Professional will collect mother and infant health information and complete the lactation questionnaire on any female patient who breastfeeds while taking Prolia through 6 months after last dose after discontinuing Prolia.

10.2.2 Safety Reporting Requirement to Regulatory Bodies

Amgen will report safety data as required in accordance with local requirements to regulatory authorities, Investigators/institutions, IRBs/IECs, 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/IEC or other relevant ethical review board of reportable events in accordance with local procedures and statutes.

11. Administrative and Legal Obligations

11.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. When Amgen amends the protocol and distributes the protocol amendment to the sites, 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 for all protocol amendments that Amgen provides to the site. The Investigator **must** send a copy of the approval letter from the IRB 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 in writing of the study's completion or early termination and send a copy of the notification to Amgen.

12. Plans for Disseminating and Communicating Study Results

Once the survey results are finalized, if applicable, a discussion will be included to address the extent to which the REMS goals related to knowledge are met, how that determination is made, and if the demonstrated understanding is below the pre-specified threshold, outline steps to achieve the desired knowledge rates (eg, enhancing REMS educational materials or outreach activities as outlined the Prolia REMS Supporting Document).

During the reporting phase, all data analyses tables and listings will be generated in Excel and provided to Amgen for inclusion for submission to FDA.

The REMS Survey methodology protocol and instrument will be submitted to FDA in both a Portable Document Format and Word Format.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data

from the participant is aware of any new information which might influence the evaluation of the benefits and risks of an Amgen product, Amgen should be informed immediately.

In addition, the investigator will inform Amgen immediately of any urgent safety measures taken by the party responsible for collecting data from the participant to protect the study participants against any immediate hazard, and of any serious breaches of this non-interventional study protocol that party becomes aware of.

12.1 Publication Policy

The results of this study will not be submitted for publication.

13. Compensation

All respondents, regardless of the method chosen to complete the survey, who complete the survey and who provide their contact information will receive a mailing to begin distribution at survey close and will be sent directly to the respondent based on the address provided during survey completion. This mailing will include:

- Thank you letter for completing the HCP KAB Survey.
- Compensation meeting a fair market value amount will be provided for their time in completing the survey.
- Correct answers to important survey questions about the safe use of Prolia.

14. References

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika* 1934;26(4):404–13.

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Patient Protection and Affordable Care Act, 42 USC §6002 (2010). Accessed October 31, 2023. http://www.gpo.gov/fdsys/pkg/PLAW-111publ148/pdf/PLAW-111publ148.pdf.

US Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Survey Methodologies to Assess REMS Goals That Relate to Knowledge: Guidance for Industry. Draft Guidance. Issued 24 January 2019.

US Food & Drug Administration. REMS Assessment: Planning and Reporting. Draft guidance. January 2019. Accessed September 29, 2023. https://www.fda.gov/media/119790/download.

15. Appendices

Appendix A. List of Stand-alone Documents

None

Appendix B. ENCePP Checklist for Study Protocols

<<A copy of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Checklist for study protocols is available at the following location: http://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml . It is to be completed and signed by the main author, as listed on the title page of the study protocol, and should be included in Appendix B. The checklist will facilitate the review of the protocol and evaluation of whether investigators have considered important methodological aspects.>>

<<In question 9.5 of the Checklist Revision 1:

- *"Study start" means "Start of data collection"*
- *"Study progress" means "Progress Report(s)"*
- *"Study completion" means "End of data collection"*
- *"Reporting" means "final report of the study results">>*

LIST OF TABLES

ANNEX 1: LIST OF STAND-ALONE DOCUMENTS

None

ANNEX 2: PARTICIPANT QUALITATIVE RESEARCH PLAN AND SCREENER

Qualitative Research to Evaluate HCP Knowledge, Attitudes, and Behavior (KAB) Survey Questions for the Prolia® (denosumab) REMS

Amgen Inc.

List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
Amgen	Amgen Inc.
APRN	Advanced Practice Registered Nurse
DO	Doctor of Osteopathy
FDA	Food and Drug Administration
HCPs	Healthcare Providers
IgG2	Immunoglobulin G2
KAB	Knowledge, Attitudes, and Behavior
MD	Doctor of Medicine
MIR	Medical Information Request
OSF	Other Safety Events
PA	Physician Assistant
PC	Product Complaint
QR	Qualitative Research
RANK	Receptor Activator of Nuclear Factor-Kappa B
RANKL	RANK Ligand
REMS	Risk Evaluation and Mitigation Strategy
SE PSP	Safety Event Project Specific Procedure
TDIs	Telephone In-Depth Interviews
UBC	United BioSource LLC
US	United States

OVERVIEW

Prolia® (denosumab) is a fully human Immunoglobulin G2 (IgG2) monoclonal antibody with affinity (equilibrium dissociation constant = 3x x10 12 M) and specificity for human receptor activator of nuclear factor-kappa B (RANK) ligand (RANKL). Prolia has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells. RANKL exists as a transmembrane or soluble protein.

RANKL is essential for the formation, function, and survival of osteoclasts, the sole somatic cell type responsible for bone resorption. Prolia binds to RANKL, preventing RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone.

Because of the increased risk of severe hypocalcemia, a comprehensive Risk Evaluation and Mitigation Strategy (REMS) was determined necessary by the United States (US) Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh the risks. Amgen Inc, (hereinafter referred to as “Amgen”) received the FDA’s approval of Prolia and the Prolia REMS on 05 March 2024.

A component of the Prolia REMS Assessment Plan is the conduct of a quantitative evaluation survey of healthcare providers (HCPs) to assess their awareness of the REMS materials, knowledge of the risks associated with Prolia, and knowledge of the requirements of the Prolia REMS. This noninterventional study is part of the Prolia REMS Assessment and is a commitment to the FDA.

In order to effectively evaluate the HCP Knowledge, Attitudes, and Behavior (KAB) Survey, qualitative research, hereafter referred to as Qualitative Research (QR), will be conducted on a subset of questions from the draft Wave 1 HCP KAB Survey with a representative sample of HCPs who are treating osteoporosis will be identified via direct outreach by a recruitment facility. The recruitment facility will utilize its nationwide proprietary database of HCPs who have expressed interest in participating in market research and opted-in to be contacted about potential research opportunities.

QR will be carried out in a double-blinded manner, ie, respondents will not know the identity of Amgen and the product under study and Amgen will not know the respondents who participated in the study. Note that in the event an HCP reports information that

meets the criteria as defined in the Safety Event Project Specific Procedure (SE PSP), the identity of the HCP may be provided to Amgen.

Feedback elicited from the QR interviews will be used to support the identification of terms, questions, or topics that may require clarification or revision based on any areas of confusion or miscomprehension reported by interviewed participants.

Upon concluding this research, a findings presentation will be delivered by United BioSource LLC (UBC), the KAB Administrator, the company responsible for conducting this research, on behalf of Amgen. Findings and recommendations from QR will be reviewed and incorporated as appropriate to update the questions and response options prior to the implementation of the Wave 1 HCP KAB Survey.

RESEARCH DESIGN

This QR plan outlines the goals and objectives, research methodology, eligibility criteria, and interview design to be used in the qualitative evaluation of the HCP knowledge, attitudes, and behaviors around the survey questions, and response options being testing for the Prolia KAB Survey.

Objectives

The objectives of this research include the following:

- Review of survey questions and response options with respect to comprehension, relevance, and clarity.
- Identify terms, questions, or topics that require clarification or revision based on areas of confusion or miscomprehension by interviewed participants.
- Evaluate participants' overall understanding of the survey questions and response options; and
- Make recommendations for potential changes to the survey questions and/or response options based on QR findings.

Methodology

The goal of the qualitative research is to conduct twelve (12), 60-minute one-on-one Telephone In-Depth Interviews (TDIs) with a representative sample of HCPs who are treating osteoporosis.

All interviews will be conducted by an experienced research moderator (hereafter referred to as "moderator") to ensure consistency between participant interviews using a detailed discussion guide. All interviews will be audio recorded with the participants' consent and subsequently transcribed.

Eligibility Criteria

Inclusion Criteria:

Include 12 HCPs who:

- Are located in the US.
- Are treating patients with osteoporosis.
- Do not work for or have immediate family who work or is a consultant for a pharmaceutical company, UBC, or the FDA.
- Who have not been debarred or otherwise sanctioned
- Have access to a computer/tablet with access to the internet during the interview.
- Are willing and able to sign an Interview Release Form to participate in the research.

Exclusion Criteria:

HCPs who do not meet all of the inclusion criteria as listed above.

Recruitment

UBC will work with a recruitment vendor to identify participants who meet eligibility (Eligibility Criteria). Recruitment will consist of direct outreach to each potential participant, utilizing various outreach methods including mail, e-mail and/or telephone calls. Up to 3 attempts will be made targeting non-responders. Eligible participants who complete the interview and would like to receive compensation can choose to receive compensation as fair market value for their time spent participating in the interview. All potential participants have the option of participating and not receiving compensation. Thank you materials can be found in Appendix 4 of this document.

Participants will be screened (Appendix A) for eligibility as outlined in the Eligibility Criteria. When a respondent meets all eligibility criteria, the recruitment vendor will:

- Collect the participant's information and schedule an interview.
- E-mail/fax/mail and collect the Interview Release Form from the participant.
- E-mail/fax/mail participant confirmation letters which include the interview date and time, the teleconference dial-in information, and detailed instructions on how to join the interview.
- Notify participants at the completion of the interview and once the Interview Release Form that s/he will be compensated for their time spent participating in this 60-minute qualitative interview process.
  - **If Physician:** CCI [redacted]
  - **If APRN (including NP)/Physician Assistant (PA):** CCI [redacted]

The recruitment vendor will only share participant information with UBC that is necessary to determine eligibility, to coordinate the research interview with participants, and or to comply with reporting of information as outlined in the SE PSP. Depending on the

information being queried, UBC may share information with Amgen to further the decision in support of this research.

If the participant does not want to be contacted about future research studies, their information will be removed from future contact attempts. If for any reason, the recruitment vendor is unsure about a participant's eligibility as it relates to this program, the recruitment vendor will contact UBC who will confirm with Amgen as needed.

INTERVIEW DESIGN

Prior to the Interview

Upon confirmation of each participant's eligibility and availability, the recruitment vendor will e-mail or fax an interview confirmation letter to each participant.

Each participant will be informed that the interview will be conducted online where the moderator will share a screen with the participant and present the materials for review. As such, the participant will be advised that a computing device of reasonable size (ie, desktop, laptop, or tablet; not a smartphone) will be needed with access to the internet at the time of the interview.

During the Interview

All participant interviews will follow a standard process and will be guided by a pre-scripted discussion guide. When the participant joins the interview, the moderator will go through introductions and disclosures with the participant. For example:

1. General introductions – The moderator will thank the participant for being part of the research and inform the participant that the interview will be audio taped only to help prepare a written report for research purposes. The moderator will reconfirm with the participant that audio taping may begin and will initiate recording upon the participant's agreement.
2. Confidentiality – The moderator will inform the participant that the information gathered is for research purposes only and s/he will not be identified by name in any reports. The moderator will assure the participants that their input and opinions will be reported in aggregate and are important to improve the program's research or educational materials.
3. Potential Adverse Event (AE), Other Safety Events (OSF), Potential Product Complaint (PC), Potential Medical Information Request (MIR), and/or Potential REMS-related Questions, Reporting – The moderator will inform the participant that should any Potential AE, PC, MIR, and/or REMS-related Questions be reported, the moderator is required to forward this information to the research sponsor and ask the participant if they are willing to waive their confidentiality for Potential AE, PC, MIR, and/or REMS-related Questions reporting purposes only.
4. Rapport building – The moderator will learn a little bit about the participant.

5. The moderator will remotely assist the participant in logging in to the secure website to review the materials via screen share.

After the above steps, the moderator will then review the associated question items with each participant. Additional details on interview content and conduct will be included in the HCP Moderator's Discussion Guide.

At the close of the interview, the participant will be thanked for his/her time and will log off of the online platform. The participant will be informed that the recruitment vendor will mail compensation in the amount determined as fair market value, if eligible, for their time and efforts. For more information regarding compensation for participation efforts please refer to Recruitment.

INTERVIEW RELEASE PROCEDURES

All participants will provide a signed Interview Release Form prior to the interview. All participants will provide verbal consent to be audio recorded. Participants will be informed that the transcribed interviews may be shared with the sponsor and regulatory agencies; however, the moderator will explain that neither the participant's name nor other identifying information will be associated with the audio recording, or the responses provided during the interview. In the event that a participant does not consent to the recording of their interview, the interview will be terminated, and another participant will be scheduled.

POTENTIAL ADVERSE EVENT, PRODUCT COMPLAINT, MEDICAL INFORMATION REQUEST, AND REMS-RELATED QUESTION REPORTING REQUIREMENTS

The SE PSP has been created to establish a process for the proper handling of potential AEs, OSF, PCs, MIRs, and/or REMS-Related Questions should personnel conducting this research become aware of such information.

While it is not the intent that any participant in QR will report information that meets the criteria of a potential AE, OSF, PC, MIR, and/or REMS-Related Question, it is possible that a participant may spontaneously report information that meets these criteria. If information pertaining to a potential AE, OSF, PC, MIR, and/or REMS Related Question is mentioned during a QR interview, a UBC QR team member will document the information and the participant's contact information, if consent to provide contact information is given. Information on all reports that may constitute a potential AE, OSF, PC, MIR, and/or REMS Related Question will be forwarded to Amgen, according to the UBC KAB SE PSP and the Amgen requirements for management and reporting such information.

QUALITATIVE ANALYSIS & REPORTING

Data from all research interviews, including transcripts, and interviewer notes, will be thoroughly reviewed by UBC staff. A systematic content analysis approach will be used to assess the participant's understanding of the select KAB survey questions and response options evaluated. Emphasis will be placed on identifying areas of ambiguity or disagreement with, and/or gaps in understanding the survey questions and/or response options, and suggested changes for clarification and revision.

The QR findings will be reported in two formats. One format will consist of a PowerPoint presentation that will include but not be limited to:

- Participants select survey questions and response options
- QR findings that place emphasis on identifying specific points of confusion, disagreement or ambiguity
- UBC recommendations based on participant feedback
- Final decisions made by Amgen

The second format consists of a final report prepared by UBC in Microsoft Word. This final Summary Report will include an overview of the goals and objectives of the research, participant inclusion/exclusion criteria, methodology, a description of the participant demographics, a high-level summary of qualitative findings, and final decisions made by Amgen as applicable on any modifications required to the survey questions and/or response options. Additionally, this final Summary Report, along with the QR Plan and Screener, Recruitment Materials, Discussion Guide used to conduct QR, Interview Transcripts, and the Findings Presentation, will be available for inclusion as part of the submission to the regulatory authorities.

As this research is qualitative and exploratory in nature with a limited sample size, the number of participants who made a particular comment about specific language in the survey questions/response options will not be quantified in the final Summary Report (eg, # of participants said that this question of the survey was easy to understand). Instead, the qualitative findings will highlight overall, common themes (eg, most participants felt that…) to help qualitatively inform any revisions to the materials.

Appendix A: Participant Online Screener

TOPIC: HCP Qualitative Research (QR)

Participant SCREENER

LIST(S): GENERAL POPULATION OF HCPS WHO ARE TREATING PATIENTS WITH A SIMILAR DISEASE STATE THAT IS USED FOR THOSE WHO MAY BE PRESCRIBING PROLIA HCPS.

SUNSHINE REPORTING IS REQUIRED.

PART 1 - INTRODUCTION FOR OUTBOUND CALLS:

[IF OUTBOUND CALL] Hello, my name is _____ and I am calling on behalf of [recruitment vendor]. May I speak with _____? **[INSERT CONTACT NAME]**

We are contacting you because we are conducting research interviews with healthcare providers to evaluate select survey questions and their response options to evaluate clarity.

[IF OUTBOUND CALL AND VOICEMAIL RECEIVED] Hello, my name is _____ and I am calling on behalf of UBC. I am calling to speak with _____. **[INSERT CONTACT NAME]**

We are contacting you because we are conducting research interviews with healthcare providers to evaluate select survey questions and their response options. If you are interested in participating, please return the call to **[INSERT PHONE NUMBER]**, ask to speak to **[INSERT SCREENER NAME]**.

[PROCEED TO PART 2 - SCREENING PREAMBLE AND SCREENING QUESTIONS]

PART 1 - INTRODUCTION FOR INBOUND CALLS:

[IF INBOUND CALL IN RESPONSE TO INITIAL OUTREACH] Thank you for your call. My name is _____. Can you please provide me with your first and last name? **[CONFIRM NAME IS ON LIST]**

[IF NAME IS ON THE LIST] I would like to confirm that you are calling about a research interview for survey questions related to a specific medication. **(WAIT FOR RESPONSE AND CONTINUE.)**

We are contacting you because we are conducting research interviews with healthcare providers to evaluate select survey questions and their response options related to a medication.

[PROCEED TO PART 2 - SCREENING PREAMBLE AND SCREENING QUESTIONS]

PART 2 - SCREENING PREAMBLE AND SCREENING QUESTIONS:

[CONTINUE FOR EITHER OUTBOUND OR INBOUND CALL]

This research interview is confidential and is part of a Food and Drug Administration requirement to further understand healthcare providers' knowledge, attitudes and beliefs

associated with a medication. It is for informational purposes only and is not an attempt to sell you anything or promote a product.

If this is a convenient time, I would like to ask you a few questions to determine if you qualify for participation in this research study. **[IF NOT CONVENIENT ASK:** When would be a good time to schedule a few minutes to go through a few screening questions? **Call back on DATE: _____ TIME: _____]**

[ONLINE SCREENER]

[Introduction]

Thank you for your interest in this research to evaluate select survey questions and their response options related to a medication.

If you qualify and agree to participate in this research study, the answers you provide to the following screening questions will be shared with UBC, the company conducting this research, and Amgen Inc, the sponsor of this survey. We respect that the privacy of your personal information is important to you.

Your answers to these survey questions will be combined with answers given by others and reported in an anonymous form to the sponsor. All the information you provide will be kept confidential in accordance with all applicable laws. Your personal information will be used if we are required to comply with a law or regulation, including without limitation, reporting payments made to healthcare providers under the Federal Physician Payment Sunshine Act. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the sponsor nor its contractors will sell or rent your information. Your privacy will be protected; however, research survey records may be inspected by the regulatory authorities. Your choice to allow the sponsor to use your information is entirely voluntary but necessary to take part in this research.

If you qualify and agree to participate, the research interview should take approximately 60 minutes and we'll work to find an available time that fits your schedule. Following completion of the research interview, you will receive compensation, if eligible, based on fair market value for your time and efforts.

1) Based on the information given, would you like to proceed with the following questions to determine if you are eligible to participate?

☐ Yes
☐ No **[TERMINATE]**

2) What type of healthcare provider are you?

☐ Doctor of Medicine (MD)
☐ Doctor of Osteopathy (DO)
☐ Advanced Practice Registered Nurse (APRN)
☐ Physician Assistant (PA)
☐ Other (Specify): _____

3) Do you see or treat patients with the following conditions?

☐ Arthritis
☐ Asthma
☐ **Osteoporosis [MUST SELECT TO CONTINUE]**
☐ Parkinson's Disease

4) In total, how many years have you been a healthcare professional? (Select one response)

☐ Less than 1 year
☐ 1 – 5 years
☐ 6 – 10 years
☐ More than 10 years

2) What is your primary specialty? (Select one response)

☐ Endocrinology
☐ Rheumatology
☐ Internal Medicine/Family Practice
☐ Other specialty, please specify _____ **[HOLD]**

[RECORD AND CONTINUE]

3) How long have you practiced as a healthcare provider (starting with the completion of your postgraduate training, if applicable)? (Select one response)

☐ Less than 1 year
☐ 1 – 5 years
☐ 6 – 10 years
☐ More than 10 years

[ATTEMPT TO RECRUIT A MIX]

1) Are you or a member of your immediate family currently employed by a pharmaceutical company, UBC, or the FDA?

☐ Yes **[TERMINATE]**
☐ No **[CONTINUE]**
☐ I don't know **[TERMINATE]**

[RECORD AND CONTINUE]

5) In which state(s) are you licensed to practice? _____
[IF MASSACHUSETTS, MINNESOTA, NEW JERSEY, AND/OR VERMONT CONTINUE TO Q5a]

5a) As a reminder, regulations exist stating that an honorarium or enticement cannot be paid to those who are licensed to practice in Massachusetts, Minnesota, New Jersey, or Vermont. Your opinion is valuable to us. Do you choose to continue and complete the interview without compensation?

☐ Yes **[CONTINUE TO Q6]**
☐ No **[TERMINATE]**

6) During the telephone interview, you will be directed to a protected website to review materials. Will you have a computer or tablet with access to the internet during the telephone interview?

☐ Yes
☐ No **[TERMINATE]**

7) Which of the following best describes the type of healthcare facility in which you work? (Select all that apply.)

- ☐ Office-based private practice (Community)
- ☐ Clinic-based private practice (Community)
- ☐ Hospital-based practice, non-teaching hospital (Community)
- ☐ Hospital-based practice, teaching hospital (Community)
- ☐ University-or-medical-school based hospital (Academic)
- ☐ Sleep Center (Academic)
- ☐ Government/VA hospital (Government)
- ☐ Other (Please specify)

8) Please select your gender.

- ☐ Male
- ☐ Female
- ☐ Non-binary
- ☐ Other (Specify): _____
- ☐ Prefer Not to Answer

ELIGIBILITY SCRIPT:

Thank you for your time; you qualify for participation in this research.
The interview will last for approximately **60 minutes**, will be conducted by telephone and online, and will be audio taped for research purposes. This research is confidential and is for informational purposes only; it will not be used for commercial purposes. Your answers will be combined with answers given by other people participating in these interviews. Your answers and all information collected during the interviews will be shared with the study team involved in these research interviews and may also be shared with the regulatory authorities. Your answers will remain anonymous (they will not be attributed to you).

If during the interview you mention a product complaint or an adverse event related to a product that is marketed by the sponsor even if you have already reported it to the sponsor or regulatory authorities, you acknowledge that the moderator will ask you to confirm if you are willing to receive follow-up from the sponsor in order to discuss this further. A product complaint or adverse event report will be provided to the sponsor.

The information within this report will only be used by the sponsor to satisfy its internal or regulatory requirements relating to the quality or safety of its product. You understand that your personal information will only be included in this report if you provide your consent.

[DISPLAY IF RESPONSE TO QUESTION 5 ≠ MASSACHUSETTS, MINNESOTA, NEW JERSEY, AND/OR VERMONT]

You are eligible to receive compensation for your time and effort for completing the interview. Upon receipt of the Interview Release Form and completion of the interview, you may elect to receive compensation based on fair market value for your time in participating:

- **If Physician:** CCI
- **If NP/PA:** CCI

Would you like to receive compensation?

□ Yes
□ No

[RECORD AND CONTINUE TO SCHEDULE]

[DISPLAY IF RESPONSE TO QUESTION 5a = YES]

Based on the response(s) to the question above, we want to remind you that you are not eligible for compensation for your time and effort in completing the Interview; but we do appreciate your participation!

[CONTINUE TO SCHEDULE]

SCHEDULING:

Now I would like to schedule your interview. These are the dates and times that are currently available. Please let me know what date and time works best with your schedule. **[INTERVIEWER: review calendar of availability to confirm interview date and time.]**

Thank you again for your time. I will send you a confirmation letter with information about the interview session, Interview Release Form, and instructions for returning these documents.

TERMINATION LANGUAGE TO BE USED THROUGHOUT

Thank you so much for your time. Based on one [or more] of your answers, you do not qualify for this research study.

STUDY SPECIFICATIONS SUMMARY

ATTEMPT TO RECRUIT 12 HCPs WHO:

- See/treat patients with osteoporosis
- Are located in the United States
- Include a mix of genders, years in practice, and practice setting
- Do not work for or have immediate family who work for a pharmaceutical company, UBC, or the FDA
- Have access to a computer/tablet with access to the internet during the interview
- Are willing and able to sign an Interview Release Form to participate in the research

ANNEX 3: HEALTHCARE PROVIDER QUESTIONNAIRE

Survey Legend

- * Indicates field is required.
- **----------** indicates beginning and end of a unique page.
- **[PAGE TITLE]** indicates new page/ screen (only specify if needed).
- **[PROGRAMMER]** is used to indicate directions to the programmer and is set in bold, red, uppercase letters between square brackets.
- **(INTERVIEWER)** is used to indicate directions to the phone interviewer and is set in bold, blue text between parentheses. This text appears when content is to be administered by phone only (for example, spontaneous AE reporting).
- **[<MODALITY>]** indicates a section is to be displayed for a specific modality (ie, Online, Phone).
- **[BEGIN <Section Description>]** and **[END <Section Description>]** represents the beginning and the end of a section (for example, Welcome Page).
- **[BEGIN INCLUSION/EXCLUSION QUESTIONS]** and **[END INCLUSION/EXCLUSION QUESTIONS]** are displayed next to responses that represent the beginning and the end of the inclusion/exclusion survey content.
- **[BEGIN KEY RISK MESSAGE AND SAFE USE QUESTIONS]** and **[END KEY RISK MESSAGE AND SAFE USE QUESTIONS]** are displayed next to responses that represent the beginning and the end of the main survey content.
- **[TERMINATE]** is displayed next to responses that should cause the survey to end. The following termination language will be programmed into the survey or read by the interviewer unless a different language is specified with the question. *Thank you very much for your time today. Based on your answer, you are not eligible to take this survey. We appreciate your interest in the survey.*
- **[RANDOMIZE LIST]** is inserted before questions to indicate to the programmer that the responses should be randomized for both the online and telephone survey. Responses such as “I don’t know/I don’t remember,” “Prefer not to answer,” All of the above” or “None of the above” will always appear at the end of the randomized responses, where applicable.
- **[KEEP IN POSITION]** Indicates that the option / choice will remain in position. Note this is only needed if the list of randomized.
- **[MAKE URL ACTIVE]** Used to indicate that the URL provided should be made into an active link.
- **[EXCLUSIVE]** Used to indicate that the option / choice should unselect all other options / choices in the question.
- 👁 indicates that the free text field will be included in the Free Text Review module.
- **[ANSWER TO Q#]** indicates dynamic text is present. This instruction should be placed on the question where the dynamic text should display. An instruction does not need to be added to the question from which the dynamic text is taken.
- **[TEXT LEN##]** indicates a single line text box with a max length of the number specified. Default is 200 unless otherwise noted.
- **[MULTI LEN##]** indicates a single line text box with a max length of the number specified. Default is 200 unless otherwise noted.

- **[NUM LEN##]** indicates a single line text box with a max length of the number specified numeric values only.
- **[DROP-DOWN LIST INPUT WITH US STATES/TERRITORY TABLE]** indicates to the programmer that the response should be a drop-down list containing the states in the table below.

Alabama	Georgia	Massachusetts	New York	Tennessee
Alaska	Guam	Michigan	North Carolina	Texas
American Samoa	Hawaii	Minnesota	North Dakota	US Virgin Islands
Arizona	Idaho	Mississippi	Northern Mariana Islands	Utah
Arkansas	Illinois	Missouri	Ohio	Vermont
California	Indiana	Montana	Oklahoma	Virginia
Colorado	Iowa	Nebraska	Oregon	Washington
Connecticut	Kansas	Nevada	Pennsylvania	West Virginia
Delaware	Kentucky	New Hampshire	Puerto Rico	Wisconsin
District of Columbia	Louisiana	New Jersey	Rhode Island	Wyoming
Florida	Maine	New Mexico	South Carolina	
	Maryland		South Dakota	

The following is used to categorize survey populations into standard geographic regions, but it is not displayed in the survey.

Geographic Distribution (based on address)[1]: Northeast, Midwest, South, and West regions

Northeast Region

New England Division - ME, NH, VT, MA, RI, CT

Middle Atlantic Division - NY, NJ, PA

Midwest Region

East North Central Division - OH, IN, IL, MI, WI

West North Central Division - MN, IA, MO, ND, SD, NE, KS

South Region

South Atlantic Division - DE, MD, DC, VA, WV, NC, SC, GA, FL

East South-Central Division - KY, TN, AL, MS

West South-Central Division - AR, LA, OK, TX

West Region

Mountain Division - MT, ID, WY, CO, NM, AZ, UT, NV

Pacific Division - WA, OR, CA, AK, HI

Other

Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam

[1] US Census Bureau, last revised 01 April 2020

[BEGIN SURVEY HELP SECTION] If you have questions or problems with the survey, please contact the Prolia Risk Evaluation and Mitigation Strategy (REMS) Knowledge, Attitudes, and Behavior (KAB) Survey Coordinating Center at 1-800-349-7192.

[END SURVEY HELP SECTION]

[BEGIN WELCOME PAGE]

Welcome! Thank you for deciding to participate in this very important survey. This survey should take approximately 25 minutes to complete. We ask that you please consider completing this survey in one sitting. Also, should you step away from the survey, the system will time out after 30 minutes from the last noticed activity.

If you are eligible to take the survey, please complete all survey questions as presented to you. If you are eligible to receive compensation and elect to receive compensation for participation in the survey (if eligible), you will be asked to provide your National Provider Identifier number (hereafter referred to as NPI number) and your contact information [eg, full name and mailing address].

To take the survey now, please have your NPI number ready. If you do not know your NPI number, click here **[OPEN www.npinumberlookup.org IN A SEPARATE BROWSER WINDOW]** to look it up then return to this browser window to continue to the survey.

In order to participate, you will need to provide your NPI number (hereafter referred to as NPI number). The purpose for collecting your NPI number is to identify healthcare providers (hereafter referred to as HCPs) so the reporting of certain payments to HCPs can be completed as part of the Centers for Medicare & Medicaid Services reporting requirements (otherwise known as the “Sunshine Act”).

You will be offered fair market value compensation in the amount of CCI for your time spent completing the survey; however, you can choose not to be paid and still complete the survey. Please be aware for the purposes of this survey, it has been determined that for HCPs who are licensed and practice in Minnesota, Massachusetts, New Jersey, or Vermont, you will not be compensated for survey participation, but you are still welcome to participate.

In order to be paid, if eligible, you will need to provide your full name, your mailing address, and your NPI number. Your contact information will be used to provide you with compensation, if eligible, the correct answers to important survey questions once

you complete the survey. Your contact information may also be used if it is required to comply with federal or state law or regulation, including without limitation, reporting compensation made to HCPs under the Federal Physician Payment Sunshine Act provisions.

Consider the following important information before you start the survey:

The application will time out after 30 minutes of inactivity.

If you are ready, click Continue to begin the survey. If you do not have enough time now, click Return Later and return to this site when it is convenient for you.

Note: Do not use the browser's Back button while entering data.

[END WELCOME PAGE]

[BEGIN SURVEY CONTENT]

[BEGIN TELEPHONE/ONLINE PREAMBLE]

Thank you for your interest in this research survey about PROLIA. **[BEGIN ONLINE]** Before you begin, **[END ONLINE] [BEGIN TELEPHONE]** Before we begin, **[END TELEPHONE]** we would like to share some important information about this survey which is being conducted by United BioSource LLC (hereafter referred to as UBC) on behalf of Amgen Inc., the license holder for Prolia (hereafter referred to as Amgen). Your participation helps to meet the requirements set forth by the United States Food and Drug Administration (hereafter referred to as US FDA) that include the assessment of awareness and understanding of the risks associated with Prolia and the mitigation strategies as outlined in the Prolia Risk Evaluation and Mitigation Strategy (hereafter referred to as REMS) goal and objectives. The survey will take approximately 25 minutes.

Survey participation is voluntary. There are no known risks to you in taking this survey. You have the option not to participate. You may refuse to take part or withdraw at any time without penalty. You will not directly benefit; however, information may be learned that could benefit others in the future. Your answers to the questions or your decision to take part in the survey will not affect your ability to prescribe Prolia. You will be informed in a timely manner if new information becomes available that may influence your willingness to participate in the survey.

How We Use Your Information

Your answers to the survey questions will be combined with answers given by other people taking the survey. All answers will be collected by UBC, compiled, and reported in anonymous form to Amgen and the US FDA. Your name will not be used in any report. If you are eligible to take the survey, complete all the survey questions, and provide your full name, NPI number, and your mailing address, you will receive compensation, if eligible, for participation in the survey. HCPs who are not permitted to receive payment based on the state in which they are licensed and practice will not receive payment but are still eligible to participate. For the purposes of this survey, it has been determined that healthcare providers who are licensed and practicing in Minnesota, Massachusetts, New Jersey, or Vermont will not be compensated for survey participation but will be welcome to participate. The amount of the compensation does not take into account the volume or value of any referrals or business otherwise generated by you. There is no cost to you.

Your name and address will be used to send your compensation, if you are determined eligible and complete all survey questions. The mailing will be sent following the close of the survey which will be on or about July 6, 2025, and will also include a Thank You Letter, and Prolia educational materials. For survey respondents who elect not to receive payment but choose to participate, or for those who are not permitted to receive payment and still participate, if you are determined eligible to participate and complete all survey questions, you will be asked to provide your full name, and your mailing address, so we can send you a copy of materials previously listed. Your contact information may also be used if it is required to comply with federal or state law or regulation, including without limitation, reporting compensation made to HCPs under the Federal Physician Payment Sunshine Act provisions.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your survey answers.

Should you choose to participate in the survey, you agree that any information you provide during the course of the survey may be used or shared with Amgen.

How We Protect Your Privacy

UBC, on behalf of Amgen, respects that the privacy of your personal information is important to you. To the extent permitted by applicable laws and regulations, the records identifying you will not be made publicly available. You will not be contacted for

marketing purposes based on the personal information you provide during the survey or based on your answers to the survey questions. Neither Amgen nor its contractors will sell, transfer, or rent your information. Please note that research survey records may be inspected by the United States Food and Drug Administration. Your choice to allow Amgen to use your information is entirely voluntary but necessary to take part in this survey.

Please be assured that your contact information and your individual responses will be kept strictly confidential. As noted above, however, information you provide will be combined with information and survey responses provided by others and shared or reported in anonymous form. By participating in the survey, you acknowledge and agree that such combined anonymous data may be shared with and used by Amgen and disclosed to the United States Food and Drug Administration By participating, you also acknowledge that the United States Food and Drug Administration may inspect the records related to this survey which may include your individual responses. The results of the survey, including your responses, may be presented at meetings or in articles written about the survey. If the results of the survey, including your research information, are published, your identity will remain confidential.

How to Learn More about This Survey

If you have questions about the survey or problems with the survey, please contact the Prolia REMS Knowledge, Attitudes, and Behavior Survey Coordinating Center at -800-349-7192.

Taking the Survey

[BEGIN ONLINE] If you are eligible to take the survey, please complete all the survey questions. Please note that once you have answered a question and moved on, you cannot go back and change your answers. Please note your survey cannot be reset if you have started answering any questions. If you exit this survey prior to completion, you will need to contact the Prolia Survey Coordinating Center for assistance in finishing the survey via telephone. If you are eligible to receive compensation and elect to receive compensation for participation in the survey you will be asked to provide your contact information. **[END ONLINE]**

[BEGIN TELEPHONE] Acronyms are being used throughout this survey for ease of reading and clarity with the questions/statements being presented. If during the course

of the survey you are uncertain of an acronym, please ask me to provide the word or words that support the acronym to you prior to moving to the next question.

Once I have read the question and you have provided an answer, I cannot go back and change the answers you have provided; therefore, please carefully respond to each question. Once you answer the first question and you end this call prior to completion, the only way to finish it is by returning a call to the Prolia REMS KAB Survey Coordinating Center to finish via telephone. If you are eligible to receive compensation and elect to receive compensation for participation in the survey you will be asked to provide your contact information.

[END TELEPHONE] Thank you for your participation in this survey.

[END TELEPHONE/ONLINE PREAMBLE]

[BEGIN INCLUSION/EXCLUSION QUESTIONS]

1.* Your agreement to participate in this survey confirms mutual understanding in connection with completion of the survey and the fair market value of the payment to be rendered in connection with those services.

Do you agree to participate in this survey about Prolia?
- ❍ Yes
- ❍ No **[TERMINATE]**

[BEGIN PREAMBLE 1]

We would like to ask for your telephone number. Providing a telephone number is optional, and it will be used to contact you only if there are questions about your survey responses. **[END PREAMBLE 1]**

a.* Do you want to provide your telephone number?
- ○ Yes
- ○ No

[DISPLAY IF Q1a = YES] TELEPHONE NUMBER:
[EDIT CHECK: NUMERIC ONLY; MUST BE 10-DIGITS]

[BEGIN PREAMBLE 2]

We would also like to ask for your email address. Providing an email address is optional. Your email address will only be used if any follow-up is required. It will not be used for any telemarketing or shared outside the staff supporting this survey. **[END PREAMBLE 2]**

1b.* Would you provide your email address?

- ○ Yes
- ○ No

[DISPLAY IF Q1b = YES] EMAIL ADDRESS: **[MULTI LEN200]**

[EDIT CHECK: MUST INCLUDE ONE "@"]

1c.* When was the last time you prescribed to a Prolia patient?

- A ❍ Less than 1 month ago
- B ❍ 1 to 3 months ago
- C ❍ 4 to 6 months ago
- D ❍ 7 months to 1 year ago
- E ❍ More than 1 year ago
- F ❍ Never
- G ❍ I don't remember **[TERMINATE]**

[DISPLAY IF Q1c DOES NOT = F]

1d.* To how many patients have you prescribed Prolia?

- A ❍ None
- B ❍ 1-5
- C ❍ 6-10
- D ❍ 10-20
- E ❍ More than 20

[DISPLAY FOLLOWING MESSAGE AFTER Q1c IF 185 OR MORE COMPLETE RESPONDENTS HAVE ANSWERED 'Never' WHERE 185 IS A CONFIGURABLE NUMBER AND THEN TERMINATE]: Thank you for your participation. At this time, we have reached our quota of surveys completed by non-prescribers of Prolia. However, if we need additional surveys completed from you at a later time, a UBC Prolia Survey Coordinating Center Associate may follow up with you via email and/or telephone.

[DISPLAY ONLY AFTER WAVE 1]

1e.* Have you ever taken part in a REMS and KAB survey about Prolia prior to today?

- ❍ Yes
- ❍ No
- ❍ I don't know

[BEGIN TELEPHONE] As a reminder, the text below is only needed if respondent asks for clarity around acronym. **[END TELEPHONE]**

*REMS = Risk Evaluation and Mitigation Strategy; KAB = Knowledge, Attitudes, and Behavior

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1f.* Have you ever taken part in a research interview (not including surveys) about Prolia prior to today? You would have participated in this research interview in July 2024.

- ❍ Yes
- ❍ No
- ❍ I don't know

2.* Are you and/or any of your immediate family members currently working for or as a consultant to Amgen, UBC, or the FDA?

- ❍ Yes **[TERMINATE]**
- ❍ No
- ❍ I don't know **[TERMINATE]**

[BEGIN TELEPHONE] As a reminder, the text below is only needed if respondent asks for clarity around acronym. **[END TELEPHONE]** *UBC = United BioSource LLC; FDA = Food and Drug Administration

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2a.* Do you have any conflicts of interest that may affect your answers to this survey?

- ❍ Yes **[TERMINATE]**
- ❍ No
- ❍ I don't know **[TERMINATE]**

[BEGIN TELEPHONE] (INTERVIEWER: IF RESPONDENT ASKS, "WHAT IS A CONFLICT OF INTEREST," LET THE RESPONDENT KNOW THAT YOU CANNOT ELABORATE ON THE REFERENCE TO CONFLICT OF INTEREST AS IT IS PARTICIPANT TO INTERPRETATION. ALL THAT CAN BE PROVIDED IS THE QUESTION AS STATED.) [END TELEPHONE]

3.* In which state or US territory do you work? **[DROP-DOWN LIST INPUT WITH STATES TABLE]**

[BEGIN REMINDER MESSAGE 2 – DISPLAY IF Q3 = Minnesota, Massachusetts, New Jersey, or Vermont]

If you are <u>licensed and practicing</u> in Massachusetts, Minnesota, New Jersey, or Vermont, just a reminder that we appreciate your participation; however, no compensation for completion of the survey will be provided.

[END REMINDER MESSAGE 2]

[DISPLAY IF Q3 DOES NOT = Massachusetts, Minnesota, New Jersey, or Vermont]

4.* If you choose to be paid for completing the survey, your full name, and your mailing address, are required for compensation. You may participate in the survey even if you choose not to be paid. Please select one option about your participation in this survey.

A ❍ I will participate in the survey and provide my contact information.
B ❍ I will participate in the survey but choose not to be paid.
C ❍ I do not wish to participate in the survey. **[TERMINATE]**

[DISPLAY IF Q3 = Massachusetts, Minnesota, Vermont, or New Jersey]

4a.* Please select one option about your participation in this survey.

A ❍ I will participate in the survey and understand I will not receive compensation.
B ❍ I do not wish to participate in the survey. **[TERMINATE]**

[END INCLUSION/EXCLUSION QUESTIONS]

5.* What type of healthcare provider are you? Please select one response.

A ❍ Doctor of Medicine
B ❍ Doctor of Osteopathy
C ❍ Advanced Practice Registered Nurse
*Includes certified nurse practitioner, clinical nurse specialist, and certified registered nurse
D ❍ Physician Assistant
E ❍ Other

[DISPLAY IF Q5 = E]

*Please specify: **[TEXT LEN200]** 👁

6.* Please provide your National Provider Identifier number. If you have not been assigned your own NPI number, please include 0000000000 in the field below. If you do have an NPI number you will need to provide it in order to be compensated.
[TEXT LEN10] [EDIT CHECK: NUMERIC ONLY; MUST BE 10-DIGITS]

6a.* Please provide your medical license number. **[TEXT LEN50]**

[BEGIN PREAMBLE 2]

The following questions are about important safety information relating to the use of PROLIA. If you do not know the answer to a question, please select 'I don't know' rather than guess the answer.

[END PREAMBLE 2]

[BEGIN KEY RISK MESSAGE AND SAFE USE QUESTIONS]

7.* Are you aware that Prolia is contraindicated in patients with hypocalcemia?

- ❍ Yes
- ❍ No
- ❍ I don't know

8.* Patients with advanced CKD (eGFR CCI [redacted]), including dialysis-dependent patients are at greater risk of severe hypocalcemia following Prolia administration.

- ❍ True
- ❍ False
- ❍ I don't know

[BEGIN TELEPHONE] As a reminder, the text below is only needed if respondent asks for clarity around acronym. **[END TELEPHONE]**
*CKD = chronic kidney disease; eGFR = Estimated Glomerular Filtration Rate

---

9.* Please select Yes, No, or I don't know for each item. Prior to initiating Prolia in patients with advanced CKD (eGFR CCI [redacted]), including dialysis-dependent patients, evaluate for the presence of CKD-MBD.

	[RANDOMIZE]	Yes	No	I don't know
A*	CKD-MBD	❍	❍	❍
B*	Anemia	❍	❍	❍
C*	Elevated A1c	❍	❍	❍

[BEGIN TELEPHONE] As a reminder, the text below is only needed if respondent asks for clarity around acronym. **[END TELEPHONE]**
*CKD = chronic kidney disease; CKD-eGFR = Estimated Glomerular Filtration Rate; MBD = chronic kidney disease-mineral bone disorder

---

10. According to the US Prescribing Information, indicate Yes, No, or I don't know for each statement. PROLIA is a RANK ligand inhibitor indicated for treatment:
[RANDOMIZE]

		Yes	No	I don't know
A*	of postmenopausal women with osteoporosis at high risk for fracture	❍	❍	❍
B*	to increase bone mass in men with osteoporosis at high risk for fracture	❍	❍	❍
C*	of glucocorticoid-induced osteoporosis in men and women at high risk for fracture	❍	❍	❍
D*	to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer	❍	❍	❍
E*	to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer	❍	❍	❍

11.* The presence of CKD-MBD markedly increases the risk of hypocalcemia.

- ❍ True
- ❍ False
- ❍ I don't know

[BEGIN TELEPHONE] As a reminder, the text below is only needed if respondent asks for clarity around acronym. **[END TELEPHONE]**
*CKD-MBD = chronic kidney disease-mineral bone disorder

12.* Please select the best answer to complete the sentence. Patients with advanced CKD (eGFR CCI [redacted], including dialysis-dependent patients, are at greater risk o ____.
[RANDOMIZE]

A ❍ severe hypocalcemia following Prolia administration
B ❍ vision loss following Prolia administration
C ❍ severe dehydration following Prolia administration
D ❍ I don't know **[KEEP IN POSITION]**

[BEGIN TELEPHONE] As a reminder, the text below is only needed if respondent asks for clarity around acronym. **[END TELEPHONE]**
*CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate

---

13.* Please select the correct answer to the following statement. According to the REMS Letter for Healthcare Providers, patients should be provided with a copy of the:

[RANDOMIZE]

A ❍ Patient Guide
B ❍ REMS Letter for Healthcare Providers
C ❍ Medication Guide for Prolia
D ❍ None of the above **[KEEP IN POSITION]**
E ❍ I don't know **[KEEP IN POSITION]**

[BEGIN TELEPHONE] As a reminder, the text below is only needed if respondent asks for clarity around acronym. **[END TELEPHONE]**

*REMS = Risk Evaluation and Mitigation Strategy

14.* According to the REMS Letter for Healthcare Providers, you are required to review the Patient Guide with each patient, including the serious risk of Prolia and the symptoms of severe hypocalcemia.

[RANDOMIZE]

❍ True
❍ False
❍ I don't know

[BEGIN TELEPHONE] As a reminder, the text below is only needed if respondent asks for clarity around acronym. **[END TELEPHONE]**

*REMS = Risk Evaluation and Mitigation Strategy

15.* According to the REMS Letter for Healthcare Providers, all Prolia patients should be advised to seek prompt medical attention if they have signs or symptoms of severe hypocalcemia.

❍ True
❍ False
❍ I don't know

[BEGIN TELEPHONE] As a reminder, the text below is only needed if respondent asks for clarity around acronym. **[END TELEPHONE]**

*REMS = Risk Evaluation and Mitigation Strategy

16.* Pre-existing hypocalcemia is <u>not</u> required to be corrected prior to initiating therapy with Prolia.

❍ True
❍ False
❍ I don't know

17.* According to the REMS Letter for Healthcare Providers, to minimize the risk of hypocalcemia in patients with advanced CKD (eGFR CCI), including dialysis-dependent patients evaluate for the presence of CKD-MBD with iPTH, serum calcium, 25(OH) vitamin D, and 1,25 $(OH)_2$, vitamin D prior to decisions regarding Prolia treatment.

- ❍ True
- ❍ False
- ❍ I don't know

[BEGIN TELEPHONE] As a reminder, the text below is only needed if respondent asks for clarity around acronym. **[END TELEPHONE]**

*CKD = chronic kidney disease CKD-MBD - chronic kidney disease-mineral bone disorder; eGFR = Estimated Glomerular Filtration Rate; OH = hydroxy; ; iPTH = intact parathyroid hormone; REMS = Risk Evaluation and Mitigation Strategy

---

18.* According to the REMS Letter for Healthcare Providers, to minimize the risk of hypocalcemia in patients with advanced CKD (eGFR CCI), including dialysis-dependent patients you should co e turnover status (ie, serum markers of bone turnover or bone biopsy) to evaluate the underlying bone disease that may present.

- ❍ True
- ❍ False
- ❍ I don't know

[BEGIN TELEPHONE] As a reminder, the text below is only needed if respondent asks for clarity around acronym. **[END TELEPHONE]**

*CKD = chronic kidney disease; eGFR = Estimated Glomerular Filtration Rate; REMS = Risk Evaluation and Mitigation Strategy

---

19.* According to the REMS Letter for Healthcare Providers, you should coordinate care with HCPs who have expertise in CKD-MBD for patients with advanced CKD.

- ❍ True
- ❍ False
- ❍ I don't know

[BEGIN TELEPHONE] As a reminder, the text below is only needed if respondent asks for clarity around acronym. **[END TELEPHONE]**

*CKD = chronic kidney disease; CKD-MBD= chronic kidney disease-mineral bone disorder; HCP = healthcare provider; REMS = Risk Evaluation and Mitigation Strategy

---

19a.* Unfortunately you selected an incorrect answer to the previous question. The REMS Letter for Healthcare Providers does state that you should coordinate care with HCPs who have expertise in CKD-MBD for patients with advanced CKD. Can you please tell us why you were not aware of this information as presented in the letter?

[MULITI LEN 200]

[BEGIN TELEPHONE] As a reminder, the text below is only needed if respondent asks for clarity around acronym. **[END TELEPHONE]**
*REMS = Risk Evaluation and Mitigation Strategy

20.* Please fill in the blank by selecting one option from the list below. According to the REMS Letter for Healthcare Providers, to minimize risk of hypocalcemia in patients with advanced chronic CKD, monitor the patients' serum calcium weekly for _____?

- ❍ weekly for the first month after Prolia administration and monthly thereafter
- ❍ one hour after Prolia administration
- ❍ every week after Prolia administration and yearly thereafter
- ❍ I don't know

[BEGIN TELEPHONE] As a reminder, the text below is only needed if respondent asks for clarity around acronym. **[END TELEPHONE]**
*CKD = chronic kidney disease; REMS = Risk Evaluation and Mitigation Strategy

---

[END KEY RISK MESSAGE AND SAFE USE QUESTIONS]

[BEGIN PREAMBLE 3]

The next set of questions is about the requirements of the Prolia REMS.

[END PREAMBLE 3]

[BEGIN TELEPHONE] As a reminder, the text below is only needed if respondent asks for clarity around acronym. **[END TELEPHONE]**
*REMS = Risk Evaluation and Mitigation Strategy

[DISPLAY IF QUESTION 1c DOES NOT = NEVER]

21.* Please respond by answering Always, Often, Sometimes, Rarely, or Never.

		Always (100%)	Often (75%)	Sometimes (50%)	Rarely (25%)	Never (0%)
	How often do you inform patients about the serious risk of Prolia?	❍	❍	❍	❍	❍

[DISPLAY Q21 If 'Often', OR 'Sometimes', OR 'Rarely', OR 'Never' ARE SELECTED]

21a.*	Please select all that apply. Please tell us why you do not always inform patients about the serious risk of Prolia?	
	❑	Appointments with my patients are not long enough to provide this information.
	❑	Another staff member in my office provides this counseling to the patient.
	❑	The patient receives a copy of the Patient Guide, which includes information about the serious risk of Prolia.
	❑	It is unnecessary since the patient receives a copy of the Medication Guide with their Prolia, which includes this information.
	❑	The Patient Guide is not in a language my patients understand.
	❑	Other

[DISPLAY IF Q21a CONTAINS("Other")]

*Please specify: **[TEXT LEN200]** 👁

22.* Please respond by answering Always, Often, Sometimes, Rarely, or Never.

		Always (100%)	Often (75%)	Sometimes (50%)	Rarely (25%)	Never (0%)
	How often you do educate patients about symptoms of severe hypocalcemia?	❍	❍	❍	❍	❍

[DISPLAY Q22 If 'Often', OR 'Sometimes', OR 'Rarely', OR 'Never' ARE SELECTED]

22a.*	Please select all that apply. Why do you not always educate patients about serious about symptoms of severe hypocalcemia?	
	❑	Appointments with my patients are not long enough to provide this information.
	❑	Another staff member in my office provides this counseling to the patient.
	❑	The patient receives a copy of the Patient Guide, which includes information about the serious risk of Prolia.
	❑	It is unnecessary since the patient receives a copy of the Medication Guide with their Prolia, which includes this information.
	❑	The Patient Guide is not in a language my patients understand.
	❑	Other

[DISPLAY IF Q22a CONTAINS("Other")]

*Please specify: **[TEXT LEN200]** 👁

23.* Please respond by answering Always, Often, Sometimes, Rarely, or Never.

		Always (100%)	Often (75%)	Sometimes (50%)	Rarely (25%)	Never (0%)
	How often do you instruct patients to seek medical attention if they have signs or symptoms of severe hypocalcemia?	❍	❍	❍	❍	❍

[DISPLAY Q23 If 'Often', OR 'Sometimes', OR 'Rarely', OR 'Never' ARE SELECTED]

23a.*	Please select all that apply. Why do you not always instruct patients to seek medical attention if they have signs or symptoms of severe hypocalcemia?	
	❑	Appointments with my patients are not long enough to provide this information.
	❑	Another staff member in my office provides this instruction to the patient.
	❑	The patient receives a copy of the Patient Guide, which includes information about seeking medical attention if they have signs or symptoms of severe hypocalcemia.
	❑	It is unnecessary since the patient receives a copy of the Medication Guide with their Prolia, which includes this information.
	❑	The Patient Guide is not in a language my patients understand.
	❑	Other

[DISPLAY IF Q23a CONTAINS("Other")]

*Please specify: **[TEXT LEN200]** 👁

23b.* Please respond by answering Very Familiar, Somewhat Familiar, Not Familiar.

		Very Familiar	Somewhat Familiar	Not Familiar
	How familiar are you with the term CKD-MBD or CKD?	❍	❍	❍

[BEGIN TELEPHONE] As a reminder, the text below is only needed if respondent asks for clarity around acronym. **[END TELEPHONE]** *CKD = chronic kidney disease; CKD-MBD= chronic kidney disease-mineral bone disorder

---

[DISPLAY IF Q23b = Very Familiar OR Somewhat Familiar]

23c.* Do you use the CKD-MBD or CKD term on regularly in practice?

- ❍ Yes
- ❍ No

[BEGIN TELEPHONE] As a reminder, the text below is only needed if respondent asks for clarity around acronym. **[END TELEPHONE]** *CKD = chronic kidney disease; CKD-MBD= chronic kidney disease-mineral bone disorder

---

[BEGIN PREAMBLE 4]

The next questions are about informational materials for Prolia and the Prolia REMS.

[END PREAMBLE 4]

[BEGIN TELEPHONE] As a reminder, the text below is only needed if respondent asks for clarity around acronym. **[END TELEPHONE]**

*REMS = Risk Evaluation and Mitigation Strategy

24.* Please select all that apply. From what sources have you received information about Prolia?

- ❑ US Food and Drug Administration
- ❑ US Prescribing Information
- ❑ Prolia Medication Guide
- ❑ Medical Journals
- ❑ Colleagues
- ❑ Professional Conferences
- ❑ Seminars
- ❑ Epocrates.com
- ❑ Physicians' Desk Reference
- ❑ PubMed
- ❑ Sales Professional
- ❑ Medical Science Liaison
- ❑ Prolia REMS Patient Guide
- ❑ Prolia REMS Letter for Healthcare Providers
- ❑ Prolia REMS Important Safety Information
- ❑ Prolia REMS website
- ❑ Prolia website
- ❑ Other

[DISPLAY IF 4 CONTAINS("Other")]

*Please specify: **[TEXT LEN200]** 👁

25.* Prior to today, were you aware of the US Prescribing Information for Prolia?

- ❍ Yes
- ❍ No

26.* Prior to today, were you aware of the Prolia Important Safety Information?

- ❍ Yes
- ❍ No

27.* Prior to today, were you aware of the Prolia REMS website?

- ❍ Yes
- ❍ No

28.* Prior to today, were you aware of the Patient Guide?

- ❍ Yes
- ❍ No

29.* Do you have any questions about the Prolia educational materials or the Prolia REMS?

- ❍ Yes
- ❍ No

[BEGIN TELEPHONE] As a reminder, the text below is only needed if respondent asks for clarity around acronym. **[END TELEPHONE]**

*REMS = Risk Evaluation and Mitigation Strategy

[DISPLAY IF Q29 = YES]

30.* What are your questions?

[MULTI LEN200] 👁

[BEGIN DEMOGRAPHICS PREAMBLE 1]

There are just a few more questions to help combine your answers with other healthcare providers' answers.

[END DEMOGRAPHICS PREAMBLE 1]

31.* In total, how many years have you been a healthcare provider?

- ❍ Less than 1 year
- ❍ 1 to 5 years
- ❍ 6 to 10 years
- ❍ More than 10 years

32.* What is your primary medical specialty?

- ❍ Endocrinology
- ❍ Rheumatology
- ❍ Internal Medicine/Family Medicine
- ❍ Other

[DISPLAY IF Q32 CONTAINS ("Other")]
*Please specify: **[TEXT LEN200]** 👁

[END SURVEY CONTENT]

[END ONLINE/TELEPHONE SURVEY CONTENT]

---------- ADVERSE EVENT/PRODUCT COMPLAINT----------

[TELEPHONE]

[BEGIN AE]

*** (INTERVIEWER: Please record if respondent spontaneously reported an adverse event, product complaint, or any other information deemed reportable during the course of this interview. Upon completion, please complete the Prolia Reportable Event Form and e-mail it to the KAB Ops Team at kab_operational_team@ubc.com and copy the Call Center Manager.)**

- ❍ Yes
- ❍ No

[END AE]
[DISPLAY REMAINDER OF PAGE IF AE = Yes]
*Enter Safety Adverse Event Verbatim **[MULTI LEN 200]** 👁

(INTERVIEWER: Indicate to the respondent that someone may call back to ask questions about the information provided during the survey.)

[BEGIN ONLINE]

33.* Click here to download the correct answers to the important survey questions for the HCP KAB Survey. **[DISPLAY** 'HCPCorrectAnswers.pdf' **IN NEW WINDOW UPON HYPERLINK SELECTION]**

Click Next to continue.

[END ONLINE]

[BEGIN ONLINE]

34.* Click here to locate all of the REMS educational materials, including the Prescribing Information and the Medication Guide for Prolia.

[DISPLAY 'https://www.proliahcp.com/risk-evaluation-mitigation-strategy' IN NEW WINDOW UPON HYPERLINK SELECTION]

Click Next to continue.

[END ONLINE]

[BEGIN CLOSING 1 – DISPLAY IF Q4 = A]

We would like to send you $175.00 as fair market value compensation for your time spent participating in the survey and the correct answers to important survey questions at the time the survey closes, which is approximately July 6, 2025. We need your full name and mailing address to do so. If you do not provide this information, you will not receive compensation, or the educational materials listed above. [END CLOSING 1]

35.* Do you agree to give us your full name and mailing address so we can send you $175.00 and the Prolia educational materials?

- ❍ Yes
- ❍ No

[DISPLAY IF Q35 = "Yes"] Please note that payment processing begins upon survey close which is targeted to be on or about July 6, 2025. Please allow 4-6 weeks for processing.

[BEGIN ONLINE] Click Next to continue. [END ONLINE]

[BEGIN CLOSING 1A - DISPLAY IF Q4 = B OR Q4a = A]

We would like to send you a copy of the correct answers to important survey questions at the time the survey closes, which is approximately July 6, 2025, but we need your full name and mailing address to do so.

[END CLOSING 1A]

36.* Do you agree to give us your full name and mailing address so we can send you a copy of the correct answers to the survey questions?

- ❍ Yes
- ❍ No

[BEGIN ONLINE] Click Next to continue. [END ONLINE]

[BEGIN CONTACT INFORMATION – DISPLAY IF 1a = YES OR 1b = YES OR Q35 = YES OR Q36 = YES]

Because you have agreed to provide your contact information, please provide the following:

The field is displayed if: [InSurveyFlow] Equal to FALSE OR [Q35 = YES OR Q36 = YES]
The required constraint only is applied if: [InSurveyFlow] Equal to True
FIRST NAME **[TEXT LEN50]**

The field is displayed if: [InSurveyFlow] Equal to FALSE OR [Q35 = YES OR Q36 = YES]
The required constraint only is applied if: [InSurveyFlow] Equal to True
LAST NAME **[TEXT LEN50]**

The field is displayed if: [InSurveyFlow] Equal to FALSE OR [Q35 = YES OR Q36 = YES]
The required constraint only is applied if: [InSurveyFlow] Equal to True
ADDRESS **[MULTI LEN200]**

The field is displayed if: [InSurveyFlow] Equal to FALSE OR [Q35 = YES OR Q36 = YES]
The required constraint only is applied if: [InSurveyFlow] Equal to True
CITY **[TEXT LEN50]**

The field is displayed if: [InSurveyFlow] Equal to FALSE OR [Q35 = YES OR Q36 = YES]
The required constraint only is applied if: [InSurveyFlow] Equal to True

STATE **[DROP-DOWN LIST INPUT WITH STATES TABLE]**

The field is displayed if: [InSurveyFlow] Equal to FALSE OR [Q35 = YES OR Q36 = YES]
The required constraint only is applied if: [InSurveyFlow] Equal to True
[EDIT CHECK: NUMERIC ONLY; MUST BE 5-DIGITS]

ZIP CODE **[TEXT LEN5]**

The required constraint only is applied if: [InSurveyFlow] Equal to True
[EDIT CHECK: NUMERIC ONLY; MUST BE 10-DIGITS] [Q6]

NPI **[TEXT LEN10]**

The field is displayed if: [InSurveyFlow] Equal to FALSE OR [Q1b = YES]
The required constraint only is applied if: [InSurveyFlow] Equal to True
[EDIT CHECK: NUMERIC ONLY; MUST BE 10-DIGITS]

TELEPHONE **[TEXT LEN10]**

The field is displayed if: [InSurveyFlow] Equal to FALSE OR [Q1c = Yes]
The required constraint only is applied if: [InSurveyFlow] Equal to True
[EDIT CHECK: MUST INCLUDE ONE "@"]
EMAIL ADDRESS: **[TEXT LEN200]**

[END CONTACT INFORMATION]

[BEGIN END OF SURVEY MESSAGE]

This is the end of the survey. If you have questions about the survey, please contact the Prolia REMS KAB Survey Coordinating Center at -800-349-7192. Thank you again for your help.

[END END OF SURVEY MESSAGE]

[END SURVEY CONTENT]

ANNEX 4: RECRUITMENT MATERIALS

Informational Letter to Healthcare Provider

[CURR_DATE]

[HEALTHCARE PROVIDER_FIRST_NAME] [HEALTHCARE PROVIDER _LAST NAME], [TITLE]

[HEALTHCARE PROVIDER _STREET_ADDR]

[HEALTHCARE PROVIDER _CITY], [HEALTHCARE PROVIDER _STATE] [HEALTHCARE PROVIDER _ZIP]

Dear [HEALTHCARE PROVIDER _FULL_NAME]:

Amgen Inc. is conducting a research survey as part of a Food and Drug Administration (FDA) requirement to find out if Healthcare Providers (HCPs) understand important safety information related to the use of Prolia. We are looking for 371 HCPs to complete the survey. The survey should take approximately 25 minutes to complete.

Eligible HCPs who complete the survey will be monetarily compensated in the amount of CCI for their time. However, please be aware that healthcare providers who work in Minnesota, Massachusetts, New Jersey, or Vermont will not be eligible to receive payment for survey participation.

Please note, however, that if you work in any of these states, you may still complete the survey without receiving compensation.

UBC will be conducting the survey on behalf of Amgen Inc.

At this time, we are letting you know that because you have been identified as having been trained per the Prolia REMS requirements.

The survey is expected to be conducted from March X, 2025 – July 6, 2025.

Sincerely,
The Prolia KAB Survey Coordinating Center

HCP Invitation Letter

[CURR_DATE]

[HEALTHCARE PROVIDER_NAME]
[HEALTHCARE PROVIDER _STREET_ADDR]
[HEALTHCARE PROVIDER _CITY], [HEALTHCARE PROVIDER _STATE]
[HEALTHCARE PROVIDER _ZIP]

Dear [HEALTHCARE PROVIDER]:

Amgen Inc. is conducting a Risk Evaluation and Mitigation Strategy (REMS) research survey as part of a United States Food and Drug Administration (US FDA) requirement to learn if Healthcare Providers (HCPs) understand important safety information related to the use of Prolia. UBC is the research firm that is conducting the survey on behalf of Amgen Inc.

- Approximately 371 HCPs, who are currently prescribing and those who have the potential to prescribe, are being asked to participate in the survey.
- HCPs identified as eligible to participate in the survey are asked to answer all of the survey questions, provide their contact information (full name and mailing address), and may be eligible for CCI as monetary compensation for their time.
- The survey should take approximately 25 minutes to complete depending on the method chosen to complete the survey.
- The survey is expected to continue through midnight on July 6, 2025.

Please be aware that HCPs who are licensed and practicing in Minnesota, Massachusetts, New Jersey, or Vermont will not be eligible to receive payment for survey participation. Please note, however, that if you work in any of these states or are a federal government employee, you may still complete the survey without receiving compensation.

Your participation in this survey is completely voluntary. Your answers to the questions or your decision to take part or not to take part in the survey will not affect your ability to prescribe Prolia. For your convenience, the survey can be completed either online via a secure website or over the telephone with a survey team associate. You are under no obligation to take this survey.

For your convenience, the survey can be completed either online via a secure website or over the telephone with a Survey Coordinating Center Associate. Please select the option that you would like to take to complete this very important survey about Prolia and proceed as noted below.

1. Scan the code below using your smartphone or using a laptop, iPad, or other computing device to visit **www.ProliaKnowledgeSurvey.com**

ENTER QR CODE

OR

2. Call **-800-349-7192**, 8 AM to 8 PM Eastern Time, Monday through Friday.

If you are completing this survey via internet or telephone, please have this letter with you at the time you take the survey. You will be asked to provide this code prior to starting the survey: **[CODE_ID]**.

We respect that the privacy of your personal information is important to you. If you choose to participate in the survey, you will be asked to provide name, address, telephone number. Your name and address will be used to send you your monetary compensation; your telephone number will be used only if there are any questions about your survey responses. In addition to the compensation, you will also receive a thank you letter and correct answers to important survey questions about the safe use of Prolia.

Your answers to the survey will be combined with answers provided by others. Your name will not be used in any report. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Your information will not be sold, transferred, or rented.

If you have any questions about this survey, please contact the Prolia KAB Survey Coordinating Center at **-800-349-7192.**

Sincerely,
The Prolia KAB Survey Coordinating Center

Direct Mail HCP Reminder Letter

[CURR_DATE]

[HEALTHCARE PROVIDER_NAME]
[HEALTHCARE PROVIDER _STREET_ADDR]
[HEALTHCARE PROVIDER _CITY], [HEALTHCARE PROVIDER _STATE]
[HEALTHCARE PROVIDER _ZIP]

Dear [HEALTHCARE PROVIDER]:

"Friendly Reminder" – **[TO BE INCLUDED IN REMINDER LETTER 1]**

"We need your help! Please respond!" [TO BE INCLUDED IN REMINDER LETTERS 2 AND 3]

You recently received a letter asking if you would consider participating in a voluntary survey associated with the use of Prolia.

On behalf of Amgen Inc., we are contacting you as a **reminder** to ask you to consider participating in this very important survey about Prolia. **At this time, some of your colleagues have already responded. Each participant in this survey is important and helps to increase accuracy and understanding of effectiveness in communicating important risks associated with Prolia. This survey will close soon, and your participation is valuable to us!**

For your convenience, the survey can be completed either online via a secure website or over the telephone with a Survey Coordinating Center Associate. Please select the option that you would like to take to complete this very important survey about Prolia and proceed as noted below.

1. Scan the code below using your smartphone or using a laptop, iPad, or other computing device to visit **www.ProliaKnowledgeSurvey.com**

ENTER QR CODE

OR

2. Call **-800-349-7192,** 8 AM to 8 PM Eastern Time, Monday through Friday.

If you are completing this survey via internet or telephone, please have this letter with you at the time you take the survey. You will be asked to provide this code prior to starting the survey: **[CODE_ID]**.

If you have any questions about this survey, please contact the Prolia KAB Survey Coordinating Center at **-800-349-7192.**

Sincerely,

The Prolia KAB Survey Coordinating Center

Healthcare Provider Thank You Letter - Compensation

[CURR_DATE]

[HEALTHCARE PROVIDER_FIRST_NAME] [HEALTHCARE PROVIDER _LAST NAME], [TITLE]
[HEALTHCARE PROVIDER _STREET_ADDR]
[HEALTHCARE PROVIDER _CITY], [HEALTHCARE PROVIDER _STATE]
[HEALTHCARE PROVIDER _ZIP]

Dear [HEALTHCARE PROVIDER _FULL_NAME]:

On behalf of Amgen Inc., we would like to thank you for taking part in the HCP KAB Survey about Prolia. To express our appreciation for your valuable time, enclosed is CCI as compensation for your time in completing this Prolia survey.

To ensure that survey participants, like yourself, have accurate information about the risks associated with Prolia, we have also enclosed the correct answers to important survey questions about the safe use of Prolia.

We know that sharing important information about Prolia is vital to ensuring that you understand all the safe use and risks associated with Prolia. You can locate all of the REMS educational materials by copying the link below and retrieving the materials from the Prolia REMS website: https://www.proliahcp.com/risk-evaluation-mitigation-strategy.

As it pertains to the CCI gift card, please read the terms and conditions included with this gift card. It is important to know that if the funds on this gift card are not used within 4 months of receipt, an administrative fee will be deducted monthly until funds are depleted. Also, please note that if you use this card for purchases online, you will be asked to include an address and you should use 933 Canyon Road, Morgantown, WV 26505. If you are trying to use this card as a debit card, you will need to set up a PIN by calling CT Payer (1-800-436-8902), however, you can use the card as a credit card without any PIN.

Sincerely,
The Prolia KAB Survey Coordinating Center

Enclosures:

- A copy of the correct answers to important survey questions about the safe use of Prolia
- CCI gift card and terms and conditions

Healthcare Provider Thank You Letter – No Compensation

CURR_DATE]

[HEALTHCARE PROVIDER_FIRST_NAME] [HEALTHCARE PROVIDER _LAST NAME], [TITLE]
[HEALTHCARE PROVIDER _STREET_ADDR]
[HEALTHCARE PROVIDER _CITY], [HEALTHCARE PROVIDER _STATE]
[HEALTHCARE PROVIDER _ZIP]

Dear [HEALTHCARE PROVIDER _FULL_NAME]:

On behalf of Amgen Inc., we would like to thank you for taking part in the HCP KAB Survey about Prolia.

To ensure that survey participants, like yourself, have accurate information about the risks associated with Prolia, we have enclosed the correct answers to important survey questions about the safe use of Prolia.

We know that sharing important information about Prolia is vital to ensuring that you understand all the safe use and risks associated with Prolia. You can locate all of the REMS educational materials by copying the link below and retrieving the materials from the Prolia REMS website: https://www.proliahcp.com/risk-evaluation-mitigation-strategy.

Sincerely,
The Prolia KAB Survey Coordinating Center

Enclosures:

- A copy of the correct answers to important survey questions about the safe use of Prolia

ANNEX 5: QUALITATIVE RESEARCH DOCUMENTS

QR Moderator Discussion Guide

QR Redacted Transcripts

QR Final Summary Report inclusive of Findings Presentation

See Section 8 for more information about these materials.

Appendix C. Sample Safety Reporting Form(s)

Observational Research Safety Reporting Form Instructions

This form is for use for observational studies that are using paper report form

General Instructions

The protocol will provide instruction on what types of events to report for the study.

***Indicates a mandatory field.**

What to report on this form:

- All adverse events (AEs) are associated with the Amgen drug irrespective of causal relationship of the event to the study drug or seriousness, unless instructed differently by the protocol.
- The following safety findings are to be reported on this form as events regardless of association with an AE:
    - medication errors, overdose, whether accidental or intentional, misuse, or abuse, involving the Amgen product
    - transmission of infectious agents
    - reports of uses outside the terms for authorized use of the product including off label use
    - occupational exposure
    - any lack or loss of intended effect of the product(s)
    - product complaint (PC)
    - adverse device effect (ADE)

The following should not be reported on this form and should be reported via the normal process set up for the study

- **pregnancy and lactation reports**

1. **Initial or Follow-up*** – Please tick the appropriate box
2. **Site Number* –** Enter your assigned site number for this study. **Participant Number* –** Enter the entire number assigned to the participant.
3. **Indicate event type* –** Tick the relevant box which applies to the event(s) you are reporting. Please note, more than one box can be ticked.
4. **Contact Details* –** Provide your name, phone, address, etc. (These contact details should be for the Vendor or Investigator)
5. **Reporter ID* –** Provide name or ID of reporter, phone, address, etc. (This could be the Investigator details if vendor details are added in section 4.
6. **HCP Contact Details (if other than reporter)* –** Provide name or ID of reporter, country, phone, address, etc.
7. **Patient* –** Enter the participants demographic information.
8. **Medical History (include primary diagnosis)* –** Enter medical history that is relevant to the reported event, not the event description. This may include pre-

existing conditions that contributed to the event, allergies and any relevant prior therapy, such as radiation. Include dates if available.

9. **Suspect Product Information (include dosing details)* –** Provide Product/Device information, Indication, start date, stop date, dose, route, frequency, Lot#, Serial#. It is important that all efforts are taken to provide the Lot number, were possible.
10. **AE, Other Safety Finding, PC/ADE Information*:**

AE Diagnosis or Syndrome*:

- If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
- If a diagnosis is not known, the relevant signs/symptoms should be entered.
- If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

Onset Date* – Enter date the AE first started rather than the date of diagnosis or hospitalization. For serious events, the start date is the date the event started, not the date on which the event met serious criteria. **This is a mandatory field.**

Resolved Date* – Enter date the AE ended. For serious events, this is not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

Hospitalization* – If the participant was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an AE. Protocol specified hospitalizations are exempt.

Serious Criteria Code* – This is a mandatory field for serious events. Select the appropriate code for the event(s) being reported

Action Taken* – State what action has been taken with suspect drug/device.

Outcome* – Enter the code for the outcome of the event at the time the form is completed if outcome is known.

Severity* – State the severity of the safety event being reported.

Relationship to Product/Device*:

Relationship to Amgen drug under study* – The Investigator must determine and enter the relationship of the event to the Amgen drug under study at the time the event is initially reported.

Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (eg, prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (eg, heating pads, infusion pumps)**

11. **Concomitant Medications* –** Indicate if there are any medications.

Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the participant is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.

Co-suspect – Indicate if the medication is co-suspect in the event.

Continuing – Indicate if the participant is still taking the medication.

Event Treatment – Indicate if the medication was used to treat the event.

12. **Relevant Laboratory Tests* –** Indicate if there are any relevant laboratory values.

For each test type, enter the test name, units, date the test was run and the results.

13. **Other Relevant Tests* –** Indicate if there are any tests, including any diagnostics or procedures.

For each test type, enter the date, name, results, and units (if applicable).

14. **Description* –** Describe Event.

Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of each page and fax the form to Amgen.

Study ID: 20240121	**AMGEN**	**Observational Research Safety Reporting Form**	**Date of Reporter Awareness:**
			Date Reported to Amgen:
	Fax reports to: Amgen Local Office	*<<populate LAO fax here or delete language>>*	

1. Initial: ☐ **Follow-up:** ☐

2. Site Number: **Subject Number:**

3. Indicate event type: ***(Please tick all that apply)***
☐ **AE/Other Safety Finding** ☐ **Product Complaint (PC)** ☐ **Adverse Device Effect (ADE)**

4. Contact Details (Vendor/Investigator)			**5. Reporter ID**		
Name	*Phone*	*Fax*	*Name or ID*	*Phone*	*Fax*
Address			*Address*		
City	*State/Province*		*City*	*State/Province*	
Postal Code	*Country*		*Postal Code*	*Country*	

6. HCP Contact Details (if other than reporter)			**7. Patient**			
Name			*Initials (optional)*	*Sex* ☐ F ☐ M	*Age (at time of event)*	*Was consent obtained to follow-up with HCP?* ☐ Yes ☐ No
Country						
Address						
City	*State/Province*	*Postal Code*	*Weight* ☐ lbs ☐ kg	*Height* ☐ in ☐ cm	*Race*	*Is patient also reporter?* ☐ Yes ☐ No
Phone	*Fax*					

8. Medical History (include primary diagnosis)	**9. Suspect Product Information (include dosing details)**				
	Product/Device:				
	Indication:				
	Start Date day month year	Stop Date day month year	Dose	Route	Frequency
Pregnant? ☐ Yes ☐ No Lactating? ☐ Yes ☐ No	Prefilled Syringe? ☐ Yes ☐ No	Lot # ☐ Unknown			Vial Size

Allergy: _____	Other Device _____	Serial # _____ ☐ Unavailable / Unknown	

10. AE, Other Safety Finding, or PC/ADE information — **HCP ONLY**

Finding (List main event first; one event per line)	**Onset Date**	**Resolved Date** *(If patient died, list date of death)* ***Cause of Death:*** *(provide autopsy report)*	**Hospitalization** Hospitalized? ☐ Yes ☐ No Prolonged Hospitalization? ☐ Yes ☐ No **Admitting dx** _____ **Date Admitted** **Date Discharged**		**Serious Criteria** **01** Fatal **02** Immediately life-threatening **03** Required/Prolonged hospitalization **04** Persistent or significant disability /incapacity **05** Congenital anomaly/birth defect **06** Other significant medical hazard **07** Non serious	**Action Taken** 1=none 2=dose reduced 3=dose increased 4=drug withdrawn 5=drug rechallenge (state outcome)	**Outcome** **01** Recovered/ Resolved **02** Recovering/ Resolving **03** Not recovered/not resolved **04** Recovered/ resolved with sequelae **05** Fatal **06** Unknown	**Severity** 1=mild 2=moderate 3=severe	**Relationship to Product /Device** Is there a reasonable possibility that this event may have been caused by the Product/ Device?	
	day month year	day month year	day month year	day month year					Product	Device
									Y N	Y N
									Y N	Y N
									Y N	Y N
									Y N	Y N
									Y N	Y N
									Y N	Y N

11. Concomitant Medications (eg, chemotherapy)

Medication Names	**Start Date** Day Month Year	**Stop Date** Day Month Year	**Co-suspect** No Yes		**Continuing** No Yes		**Dose**	**Route**	**Frequency**	**Treatment Meds**

12. Relevant Laboratory Values (include dates, allergies, and any relevant prior therapy)

Date Day Month Year	**Test**										
	Unit										

13. Other Relevant Test (diagnostics and procedures)

Date Day Month Year	**Additional Tests**	**Results**	**Units**

14. Description: Provide chronological summary and details of AE symptoms, PC or ADE that are listed in section 10 (signs, diagnosis, treatment, concomitant medications including those used to treat event).

Appendix D. Pregnancy and Lactation Notification Forms

AMGEN® Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20240121

Study Design: ☐ Interventional ☒ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ Site # _____

Phone (____)_____ Fax (___)_____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Gender: ☐ Female ☐ Male Subject age (at onset):____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd___/ yyyy_____

Has the pregnant female already delivered? ☐Yes ☐No ☐Unknown ☐N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐ Yes ☐No ☐Unknown ☐N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

Confidential Medical and Scientific Affairs

AMGEN Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/ Study Number: 20240121

Study Design: ☐ Interventional ☒ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

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Appendix E. Correct Answer Document

The correct answers to the key risk message questions can be found below.

Correct Responses to Select PRESCRIBER Survey Questions about Important Safety Messages for Prolia® (denosumab)

Questions	Desired Response
Are you aware that Prolia is contraindicated in patients with hypocalcemia?	**Yes**
Patients with advanced CKD (eGFR[CCI] , including dialysis-dependent patients severe hypocalcemia following Prolia administration.	**True**
The presence of CKD-MBD markedly increases the risk of hypocalcemia.	**True**
Please select the best answer to complete the sentence. Patients with advanced CKD (eGFR[CCI]), including dialysis-dependent patients f _____.	**severe hypocalcemia following Prolia administration**
Pre-existing hypocalcemia is not required to be corrected prior to initiating therapy with Prolia.	**False**
Please select Yes, No, or I don't know for each item. Prior to initiating Prior to initiating Prolia in patients with advanced CKD (eGFR[CCI]), including dialysis-dependent patients, evaluate for the presence of CKD-MBD.	
CKD-MBD	**Yes**
According to the REMS Letter for Healthcare Providers, to minimize the risk of hypocalcemia in patients with advanced CKD, (eGFR[CCI] , including dialysis-dependent p e presence of CKD-MBD with iPTH, serum calcium, 25(OH) vitamin D, and 1,25 $(OH)_2$, vitamin D prior to decisions regarding Prolia treatment.	**True**
According to the REMS Letter for Healthcare Providers, to minimize the risk of hypocalcemia in patients with advanced CKD (eGFR[CCI] , including dialysis-dependent patients you should consider assessing bone turnover status (i.e., serum markers of bone turnover or bone biopsy) to evaluate the underlying bone disease that may present.	**True**
According to the REMS Letter for Healthcare Providers, you should coordinate care with HCPs who have expertise in CKD-MBD for patients with advanced CKD.	**True**
Please fill in the blank by selecting one option from the list below. According to the REMS Letter for Healthcare Providers, to minimize the risk of hypocalcemia in patients with advanced chronic CKD, monitor the patients' serum calcium weekly for _____?	**weekly for first month after Prolia administration and monthly thereafter**
Please select the correct answer to the following statement. According to the REMS Letter for Healthcare Providers, patients should be provided with a copy of the:	**Patient Guide**
According to the REMS Letter for Healthcare Providers, you are required to review the Patient Guide with each patient, including	**True**

Questions	Desired Response
Are you aware that Prolia is contraindicated in patients with hypocalcemia?	**Yes**
Patients with advanced CKD (eGFR[CCI], including dialysis-dependent patients are at greater risk of severe hypocalcemia following Prolia administration.	**True**
The presence of CKD-MBD markedly increases the risk of hypocalcemia.	**True**
Please select the best answer to complete the sentence. Patients with advanced CKD (eGFR [CCI]), including dialysis-dependent patients, are at greater risk of _____.	**severe hypocalcemia following Prolia administration**
Pre-existing hypocalcemia is not required to be corrected prior to initiating therapy with Prolia.	**False**
the serious risk of Prolia and the symptoms of severe hypocalcemia.	
According to the REMS Letter for Healthcare Providers, all Prolia patients should be advised to seek prompt medical attention if they have signs or symptoms of severe hypocalcemia.	**True**

If you have questions or are unclear about any of these responses, please refer to the Full Prescribing Information and the Medication Guide for Prolia.

Approval Signatures

Document Name:	Protocol Conditionally Approved denosumab 20240121
Document Description:	20240121 Prolia Original Protocol updated post ORRG Meeting for comp pub then Conditional Approval
Document Number:	CLIN-000353943
Approval Date:	17 Sep 2024
Type of Study Protocol:	Conditionally Approved
Protocol Amendment No.:	

Document Approvals	
Reason for Signing: Functional Area	Name: PPD Date of Signature: 17-Sep-2024 15:55:47 GMT+0000