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 3.0
Date of last version of the protocol	31 March 2025
EU Post Authorization Study (PAS) Register No	
Active Substance	Denosumab
Medicinal Product	Prolia
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 survey knowledge domains 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] $<$ 30 mL/min/1.73 m^2) (Survey Knowledge Domain 1). HCPs must understand the need to assess for presence of chronic kidney disease-mineral bone disorder (CKD-MBD) before initiating Prolia Survey Knowledge Domain 2). The survey will begin with screening questions followed by survey knowledge domain 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	[redacted] PhD Global Safety Director Amgen Inc.

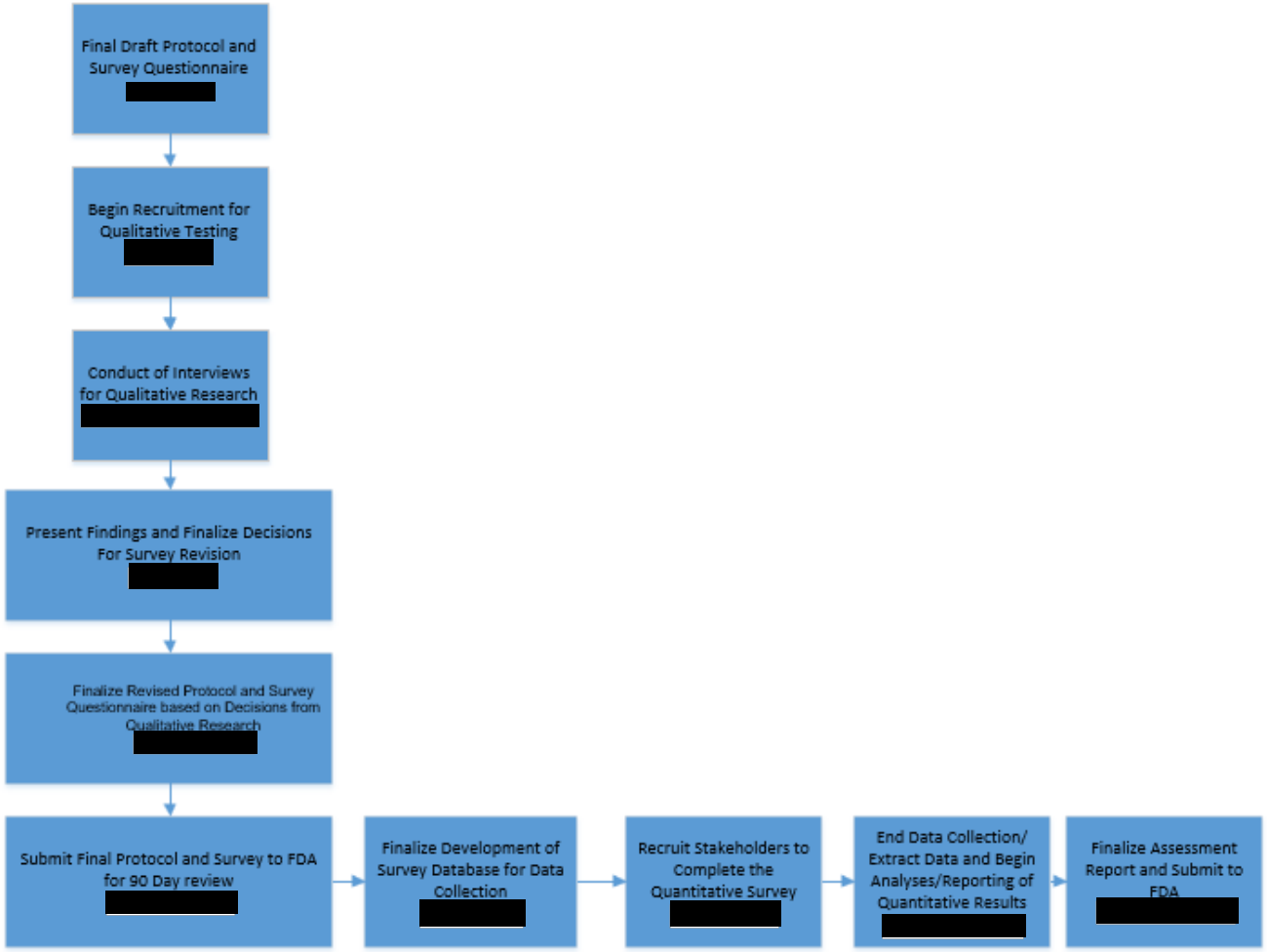
This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

Protocol Version	Date of Protocol	Page Header Date
Original, Version 1.0 Version 2.0	15 August 2024 17 January 2025	15 August 2024 17 January 2025
Version 3.0	31 March 2025	31 March 2025

Confidentiality Notice

Study Design Schema

Wave 1 HCP KAB Survey Projected Timeline



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2. List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
Amgen	Amgen Inc.
APRN	Advanced Practice Registered Nurse
CAPTCHA	Completely Automated Public Turing Test to Tell Computers and Humans Apart
CfOR	Center for Observational Research
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
[redacted]	
SOP	Standard operating procedure
UAT	User Acceptance Testing
[redacted]	
URL	Uniform Resource Locator
US	United States

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3. Responsible Parties

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

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. (hereinafter 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:

a) the need to assess the 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 the assessment of HCPs knowledge of:

a) Risk of severe hypocalcemia in patients with advanced CKD (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2)
b) Need to assess for presence of CKD-MBD before initiating Prolia

The survey will begin with screening questions followed by survey knowledge domain 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 (hereinafter 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 survey knowledge domains to support the objectives are as follows:

- Survey Knowledge Domain 1: HCPs must understand the risk of severe hypocalcemia in patients with advanced CKD (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2).
- Survey Knowledge Domain 2: HCPs must understand the need to assess for presence of CKD-MBD before initiating Prolia.

The survey questions associated with each survey knowledge domain 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 [redacted] 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 to 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]

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, [redacted], 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 survey knowledge domain 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 survey knowledge domains communicated through the Prolia REMS. Select survey questions were pre-tested via QR and submitted for FDA review on 27 September 2024.

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

These include:

- Medical degree of respondent

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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.

  - 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 survey knowledge domains:

- 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 survey knowledge domains 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 survey knowledge domain, 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 survey knowledge domain 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	31 March 2025
Start of Data Collection	12 March 2025
Wave 1 Assessment Report due to FDA	05 September 2025
Wave 2 Assessment Report due to FDA	05 March 2027
Wave 3 Assessment Report due to FDA	05 March 2031
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 < 30 mL/min/1.73 m^2) • The need to assess for presence of CKD-MBD before initiating Prolia	The number of HCPs who provide at least 80% or more correct responses for at least 80% of the overall questions for each survey knowledge domain.
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 [redacted] 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, [redacted], or the FDA.
- Respondents who report having a conflict of interest.

- Follow-up

  Not Applicable (N/A)

- Variables

The survey knowledge domains, which will be evaluated in this KAB Survey, include the following:

Survey Knowledge Domain 1: HCPs must understand the risk of severe hypocalcemia in patients with advanced CKD.

Survey Knowledge Domain 2: HCPs must understand the need to assess for presence of CKD-MBD before initiating Prolia.

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 380 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 5,000 to be included in each Batch resulting in a total of 8 Batches of 5,000,

and Batch 9 to include 2,000 HCPs. The first Batch of 5,000 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 190 completed surveys from prescribers and 190 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. 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 (hereinafter 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] $<$ 30 mL/min/1.73 m^2)
b) Assess knowledge of the need to assess for presence of CKD-MBD before initiating Prolia

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 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. All CIs around the percentages will be exact binomial 2-sided 95% CIs calculated according to the method of Clopper-Pearson method (Clopper and Pearson, 1934). 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 survey knowledge domains 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 survey knowledge domains 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:

- Survey Knowledge Domain 1: HCPs must understand the risk of severe hypocalcemia in patients with advanced CKD.
- Survey Knowledge Domain 2: HCPs must understand the need to assess for presence of CKD-MBD before initiating Prolia.

7.2 Secondary

Not Applicable (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 [redacted] 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 survey knowledge domains 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 was included in ANNEX 5 for final submission of the document submitted to the FDA on 27 September 2024.

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 [redacted] 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	~ 07 June 2024
QR	10 June 2024 - 29 August 2024

Milestones	Planned Date[1]
Protocol and Survey Revision Post QR	25 July 2024 - 12 September 2024
Protocol and Survey Submission to FDA – 90-day review	27 September 2024 - 26 December 2024[2]
[redacted] Knowledge Survey System Build	~ 02 January 2025 - 12 March 2025
Distribution of Pre-Notification Letter	~ 01 March 2025
[redacted] Knowledge Survey System in Production (Survey Launch)	12 March 2025[3]
Start of Data Collection Period	12 March 2025
Distribution of Initial Survey Invitation	~ 02 April 2025
First Reminder Mailing (alternating modalities as applicable)	~ 23 April 2025
Second Reminder Mailing (alternating modalities as applicable)	~ 14 May 2025
Outbound Calling to Non-Responders	Not Available[5]
Third Reminder Mailing (alternating modalities as applicable)	~ 16 June 2025
Fourth Reminder Mailing (alternating modalities as applicable)	~ 30 June 2025
End of Data Collection	05 July 2025
Data Processing and Report Development	06 July 2025 - 18 August 2025
Final Wave 1 Assessment Report to FDA	05 September 2025[4]

FDA = Food and Drug Administration; QR = Qualitative Research; [redacted]
[1] Dates are participant to change based on receipt of FDA comments.
[2] [redacted] 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, [redacted], or the FDA.
- 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

[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.

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 survey knowledge domains communicated through the Prolia REMS.

The survey knowledge domains, which will be evaluated in this KAB Survey, include the following:

- Survey Knowledge 1: HCPs must understand the risk of severe hypocalcemia in patients with advanced CKD.
- Survey Knowledge 2: HCPs must understand the need to assess for presence of CKD-MBD before initiating Prolia.

Survey questions will be pre-tested via QR prior to submission for FDA review as noted in Table 1 above. The survey knowledge domain questions can be found in Table 2 and Table 3. below.

Table 2. Survey Knowledge Domain 1

HCPs must understand the risk of severe hypocalcemia in patients with advanced CKD.		
Question Number	**Questions**	**Desired Response**
[redacted]		

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

Table 3. Survey Knowledge Domain 2

HCPs must understand the need to assess for presence of CKD-MBD before initiating Prolia.		
Question Number	**Questions**	**Desired Response**
[redacted]		

HCPs must understand the need to assess for presence of CKD-MBD before initiating Prolia.
[redacted]

To achieve the established knowledge threshold of at least [redacted], 4 of the 5 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 survey knowledge domains:

- 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 survey knowledge domains 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 survey knowledge domain, 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 January 2025 is approximately 42,000 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 1-5 will include 5,000 HCPs and Batch 9 will include the remaining 2,000 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, 380 completed surveys 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 5,000 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 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 [redacted] 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 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 [redacted] Knowledge Survey System maintains an audit trail containing date and time stamps.

The security of the application requires physical and logical security. The [redacted] 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. [redacted] will thoroughly validate and document the testing of the [redacted] 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 [redacted] 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 "[redacted] Login" and enter their [redacted] 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 [redacted] 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 [redacted] 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 in 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 survey knowledge domain. 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. [redacted] shall ensure that

the DCTs (the surveys) are securely stored at [redacted] on a secure server to prevent access by unauthorized third parties.

[redacted] 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, [redacted] agrees to keep all study-related records. The records should be retained by [redacted] according to local regulations or as specified in the Fully Executed Statement of Work, whichever is longer. [redacted] must ensure that the records continue to be stored securely for so long as they are retained.

If [redacted] 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 [redacted] and Amgen have expressly agreed to a different period of retention via a separate written agreement. Records must be retained for longer than 15 years if required by applicable local regulations.

[redacted] 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 1 survey knowledge domain 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 survey knowledge domain. 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. 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. 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.

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 [redacted] has been set. This prespecified threshold aligns with the FDA general guidance that [redacted] or higher should be the general standard for each REMS survey knowledge domain.

Example Table Output 1: Secondary Analysis of Survey Knowledge Domain 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 Survey Knowledge Domain 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 Survey Knowledge Domain 1, the respondent must have answered 4 of the 4 questions correctly.

8.7.6 Primary Analysis

Primary analyses are performed for all survey knowledge domain questions and will be stratified by prescriber versus non-prescriber. Responses from all questions/items from each survey knowledge domain will be summarized by counts and percentages. The primary analysis for a survey knowledge domain evaluates the rate for each correct response to each individual question/item defined by the survey knowledge domain. "Select all that apply" questions will be counted as a single correct response if the respondent selects [redacted] 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 Survey Knowledge Domain Table 2 and Table 3.. 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 survey knowledge domains 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 survey knowledge domain (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 Survey Knowledge Domain 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 survey knowledge domain, defined as answering [redacted] or more questions/items in a survey knowledge domain correctly. "Select all that apply" questions are handled as described in Section 8.7.6. The proportion of respondents who demonstrated understanding of the survey knowledge domain will be presented with 95% CIs. Additionally, the number and percentages of respondents who demonstrated understanding of all survey knowledge domains will be provided with 95% CIs. In this analysis, the proportion of respondents who demonstrated an understanding of the survey knowledge domain will be presented with 95% CIs. The REMS will be considered meeting its goals if the lower bound of the CIs of Survey Knowledge Domain 1 and Survey Knowledge Domain 2 receive a demonstrated understanding of [redacted] or above. Additionally, the number and

percentages of respondents who demonstrated understanding of all survey knowledge domains 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 [redacted] or higher for each survey knowledge domain. 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 survey knowledge domain questions and the demonstrated understanding of each survey knowledge domain 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 Completed Surveys (Primary Population) for each survey knowledge domain 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 survey knowledge domain 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. Based on hypothesis testing, the lower bound of the CIs will be utilized to assess knowledge of all HCPs.

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 190 completed surveys from prescribers and 190 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 4 shows the precision of the estimated level of understanding for the survey knowledge domains identified for HCPs with exact binomial 2-sided 95% CIs for a sample size of 380 completed surveys.

Table 4. Precision of Estimated Rates of Understanding with a Sample Size of 380 (2-sided 95% CI)

Estimated Rate	Actual Number of Correct Responses	Lower Limit	Upper Limit	Precision	Margin of Error
[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 [redacted] Knowledge Survey System programming will be reviewed by [redacted] 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 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 Internal Validity of Study Design

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, [redacted], 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 [redacted] 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 [redacted]. 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 [redacted] in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. [redacted] 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, [redacted] 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. [redacted] 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 5 below.

Table 5. 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)	• Within 1 business day from when Vendor first becomes aware of the event

• 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	
• 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 D) 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.

Nair I., Patel B. (2014). Attain 100% Confidence Limits in Your Confidence Interval. Proceedings for PharmaSUG Conference 2014. Available at https://www.pharmasug.org/proceedings/2014/IB/PharmaSUG-2014-IB05.pdf.

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

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

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

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

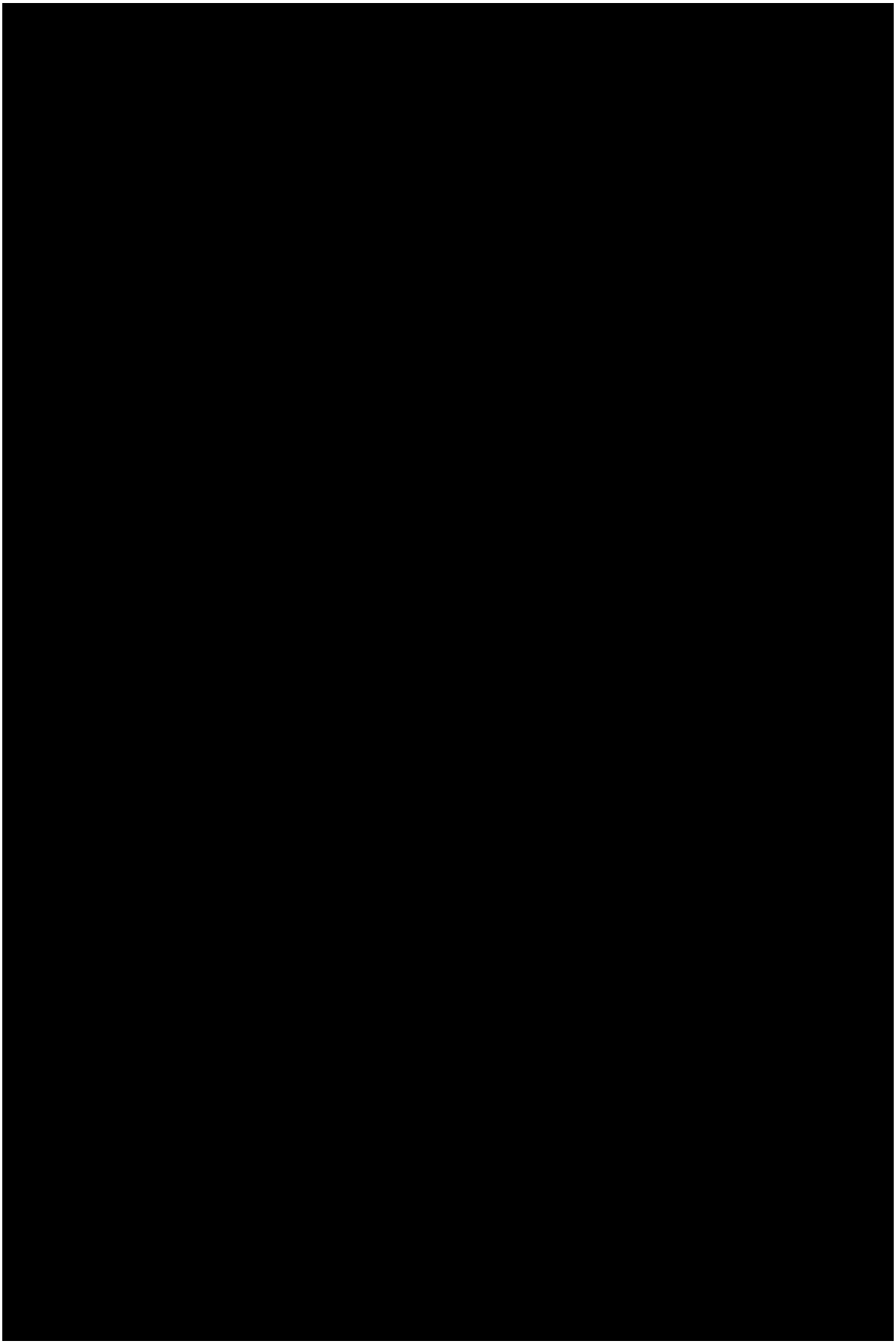
This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety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

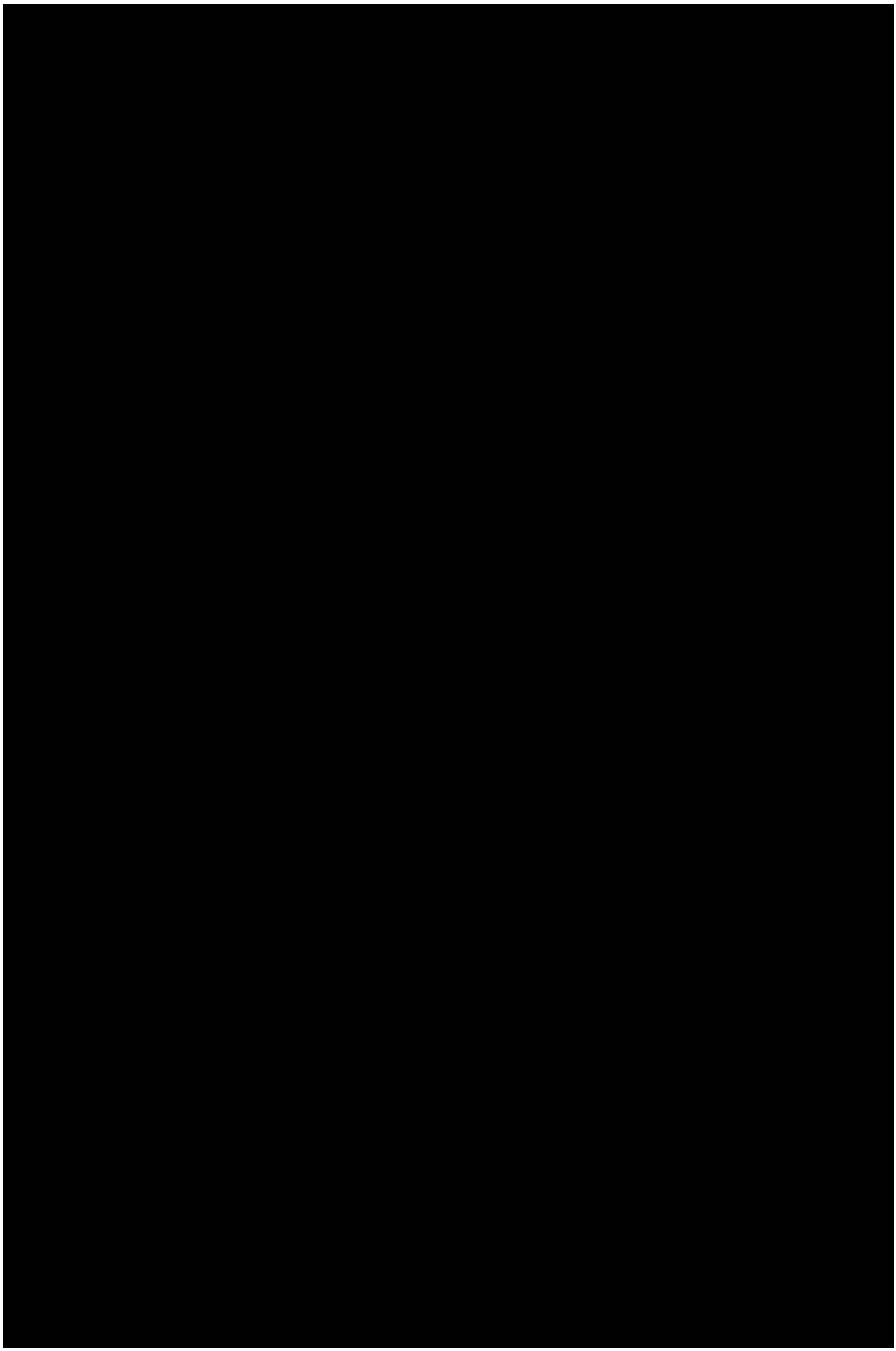
Study title: Periodic Knowledge, Attitudes, and Behavior (KAB) Survey of Certified Prescribers to Assess Understanding of the Risks with the Prolia Risk Evaluation and Mitigation of Strategy (REMS)

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

[redacted]

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





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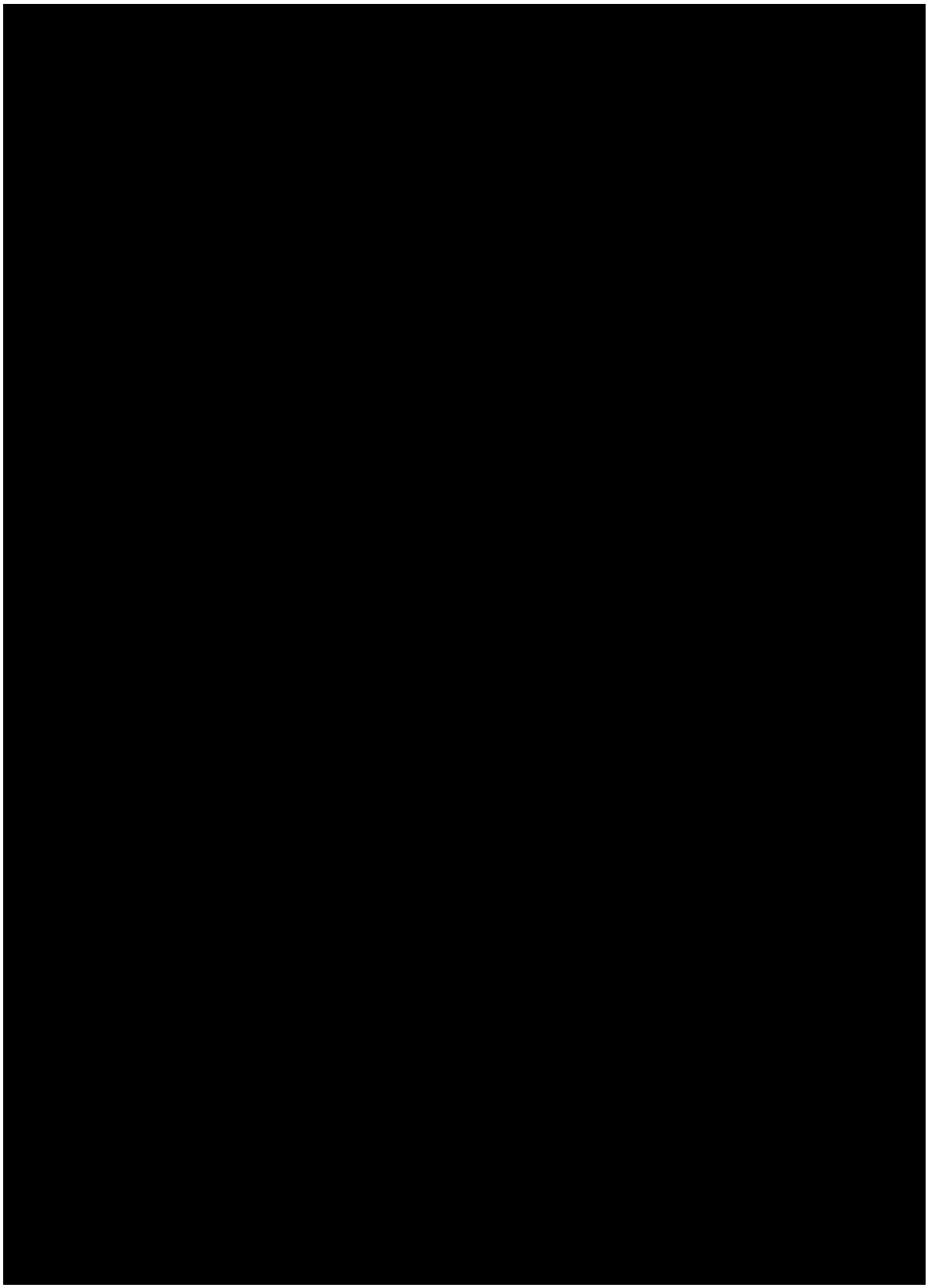
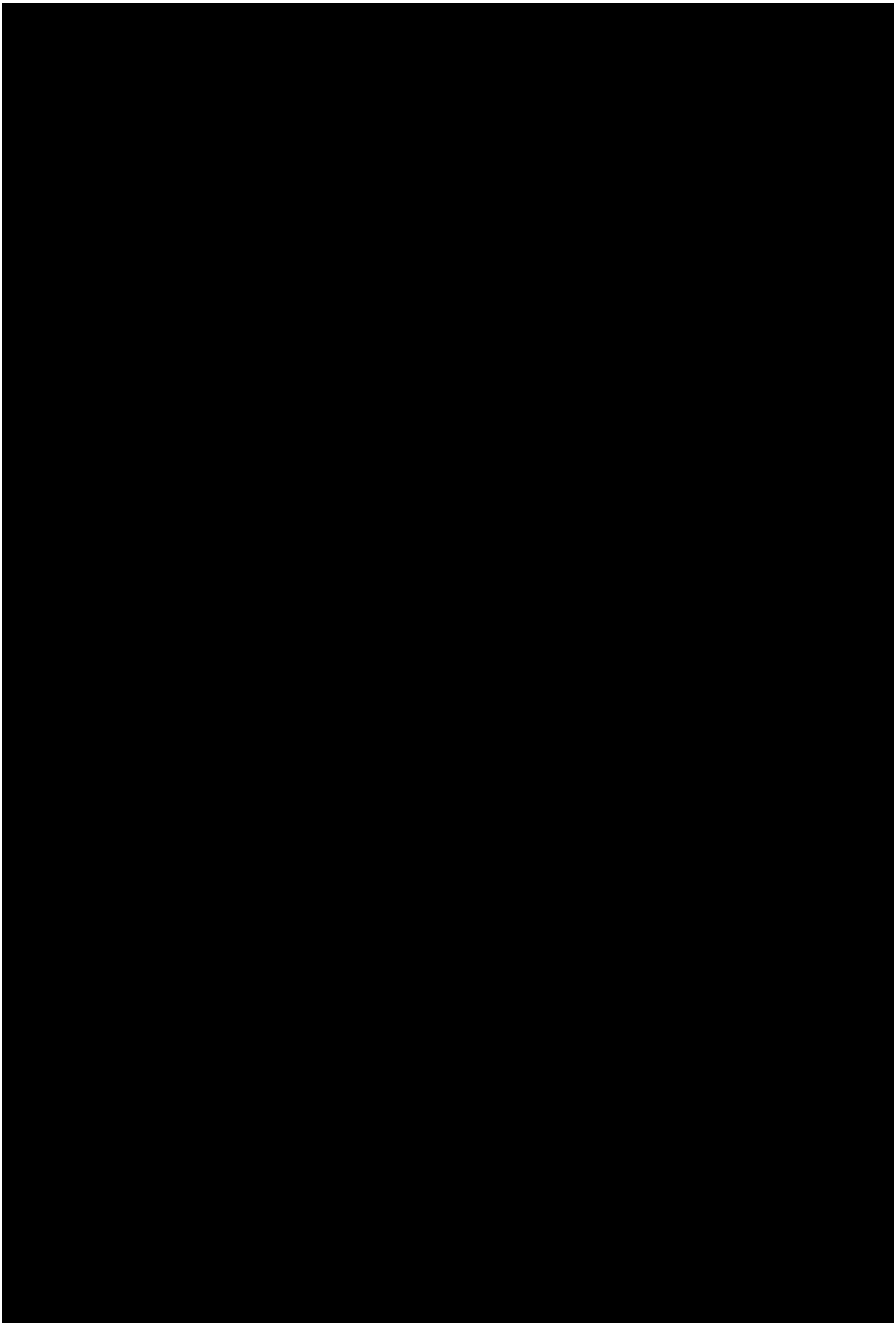




[redacted]

Comments:

Name of the main author of the protocol: [redacted]

Date: 16/March/2024

Signature: [redacted]

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.

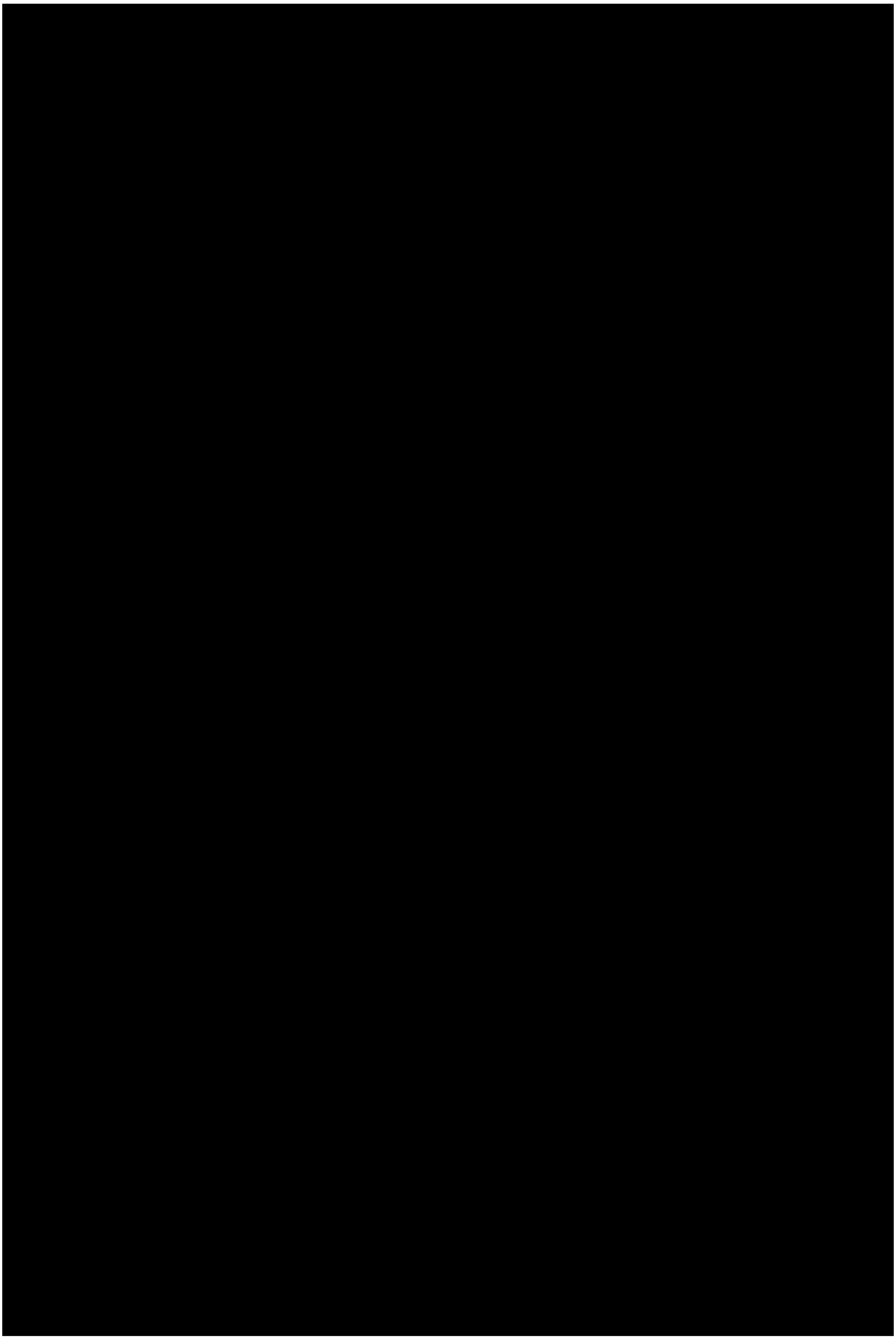
Removed to allow unbiased data

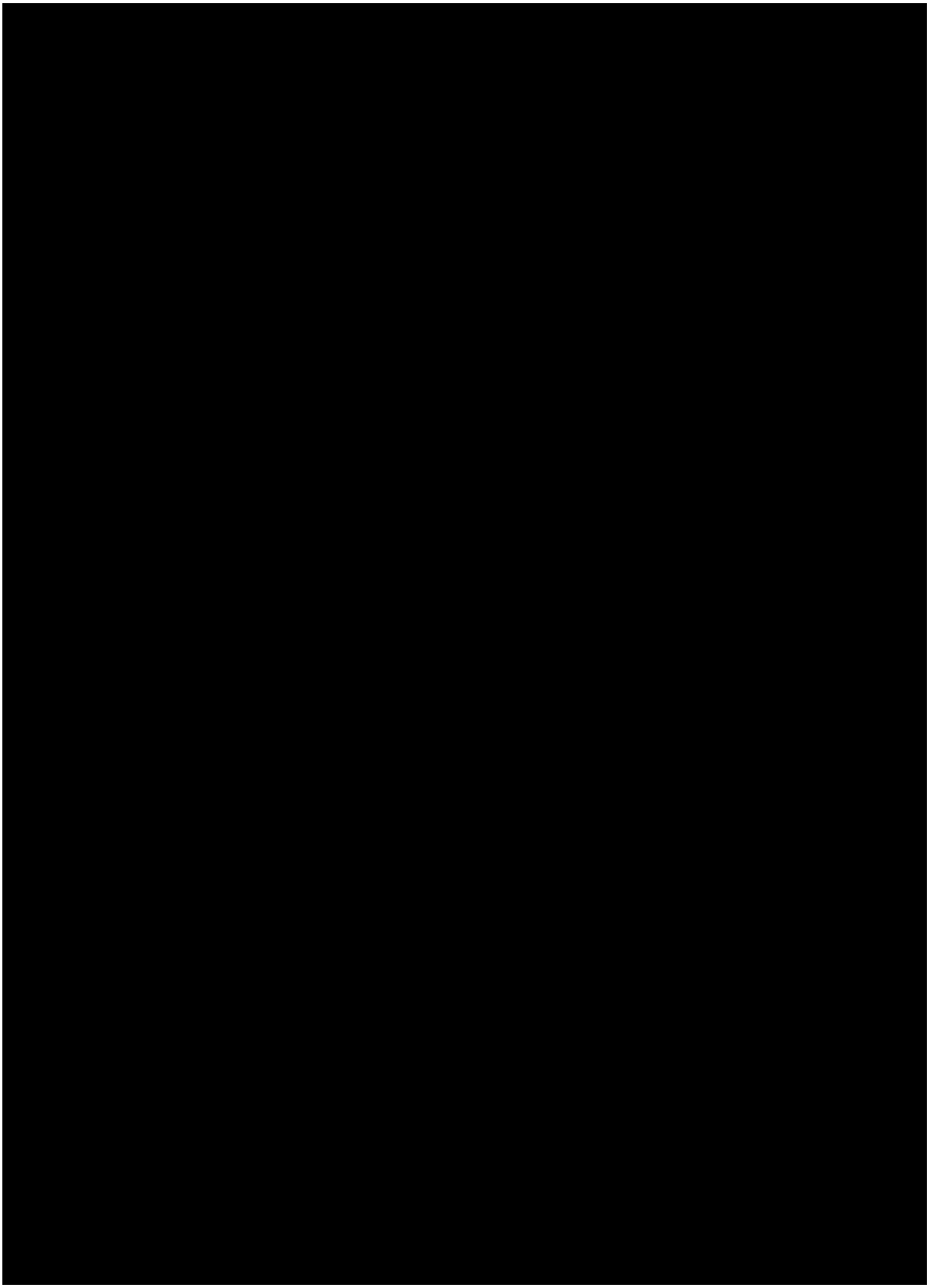
ANNEX 4: RECRUITMENT MATERIALS

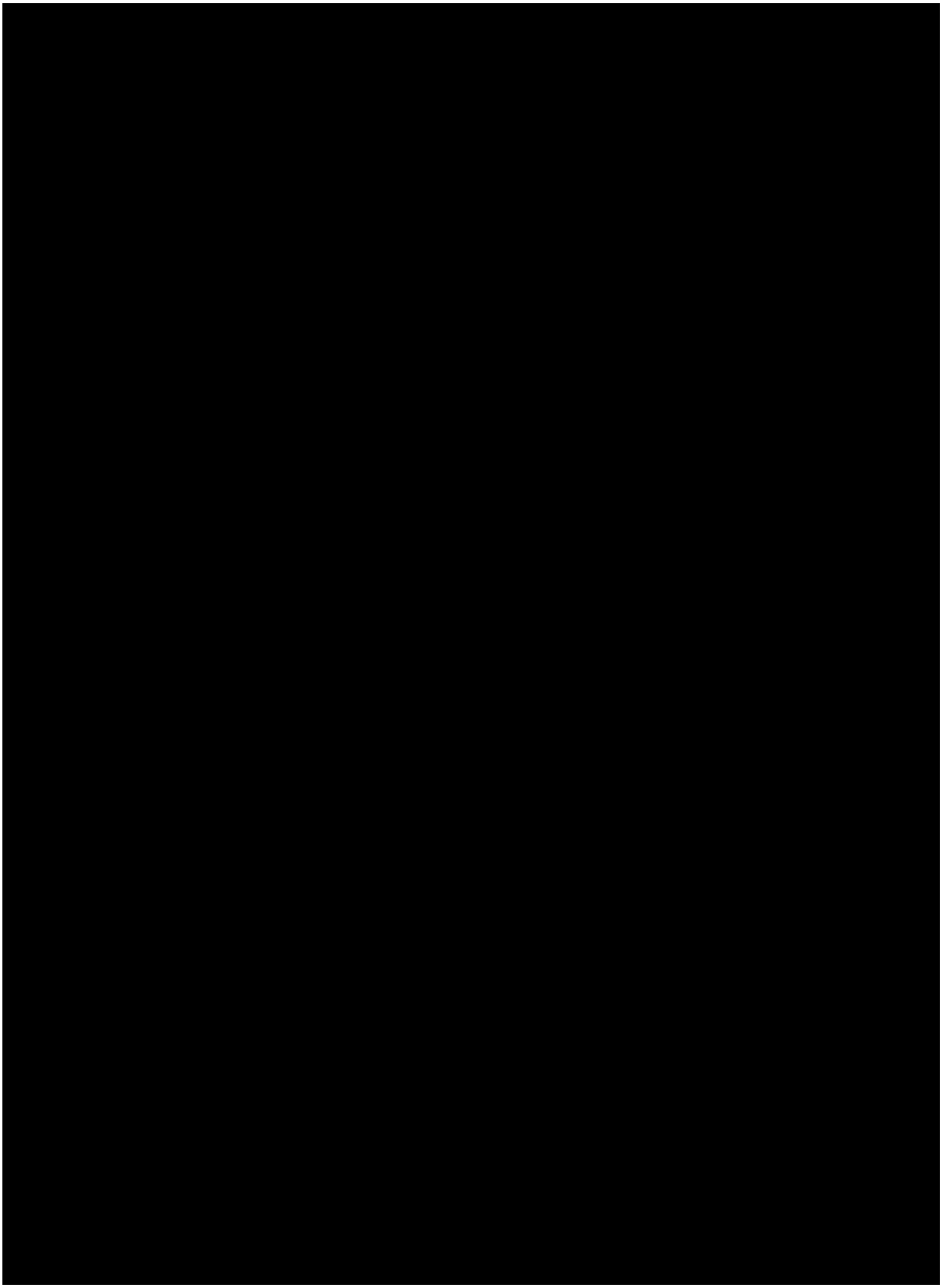
Removed to allow unbiased data.

ANNEX 5: QUALITATIVE RESEARCH DOCUMENTS

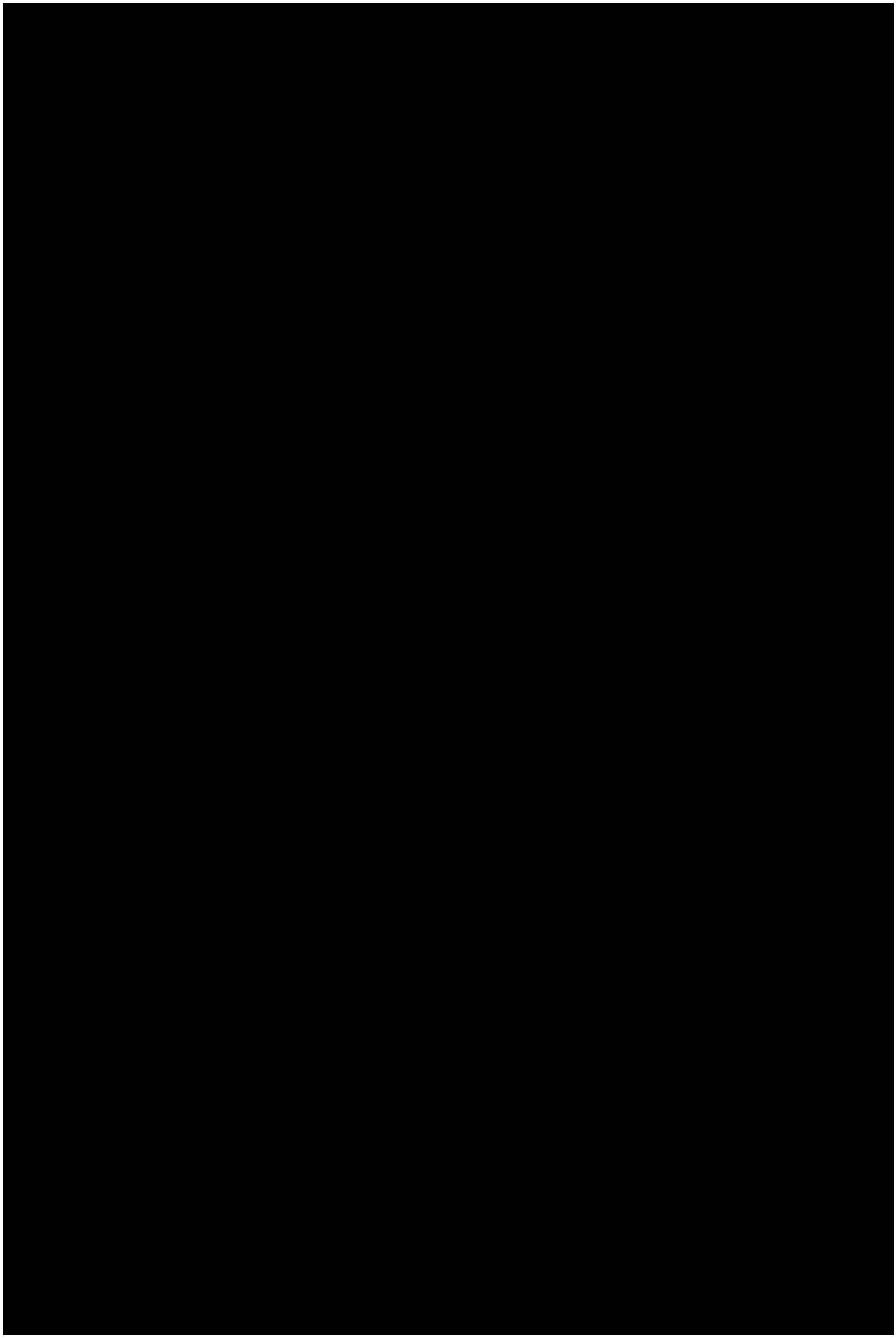
Removed to allow unbiased data.

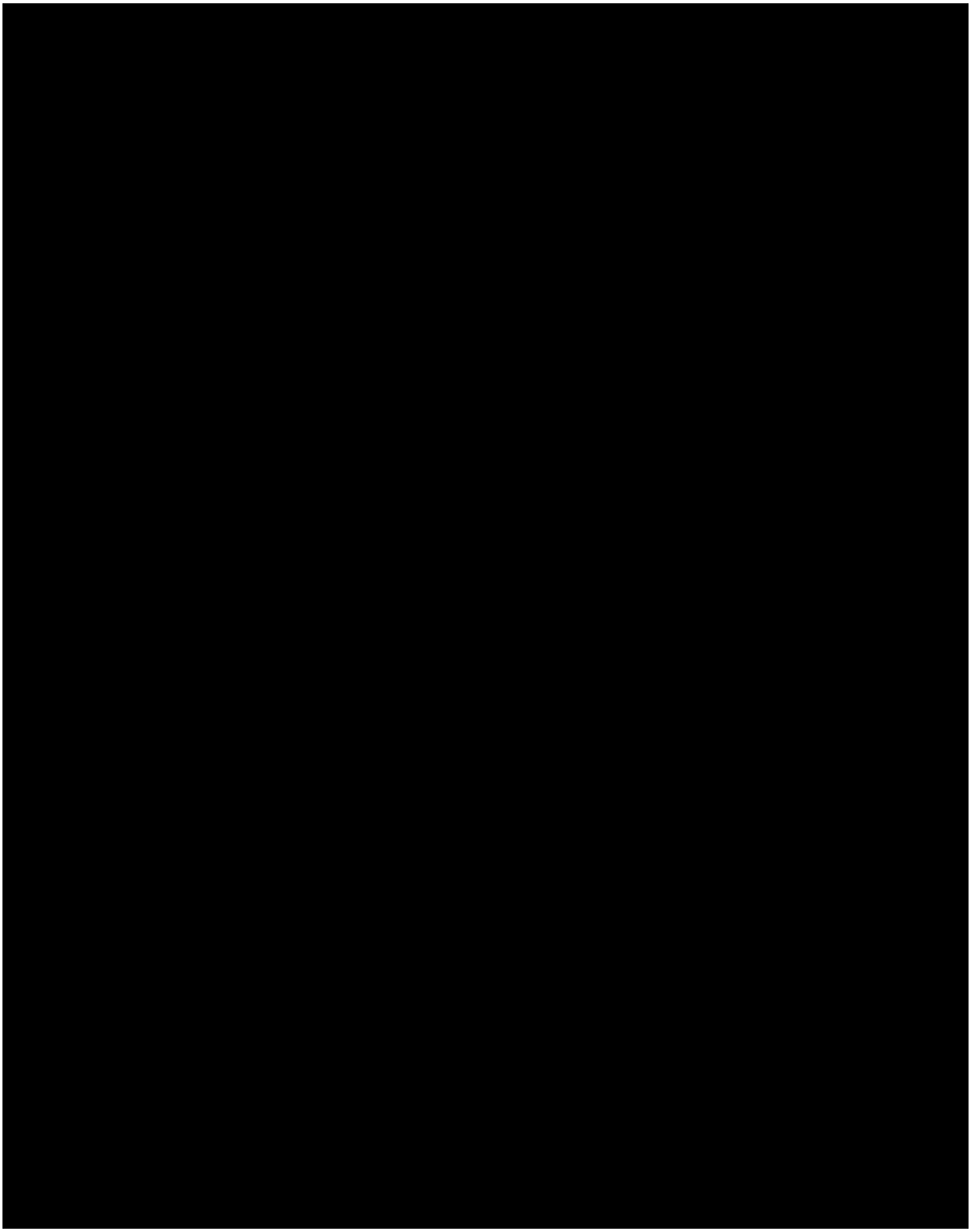


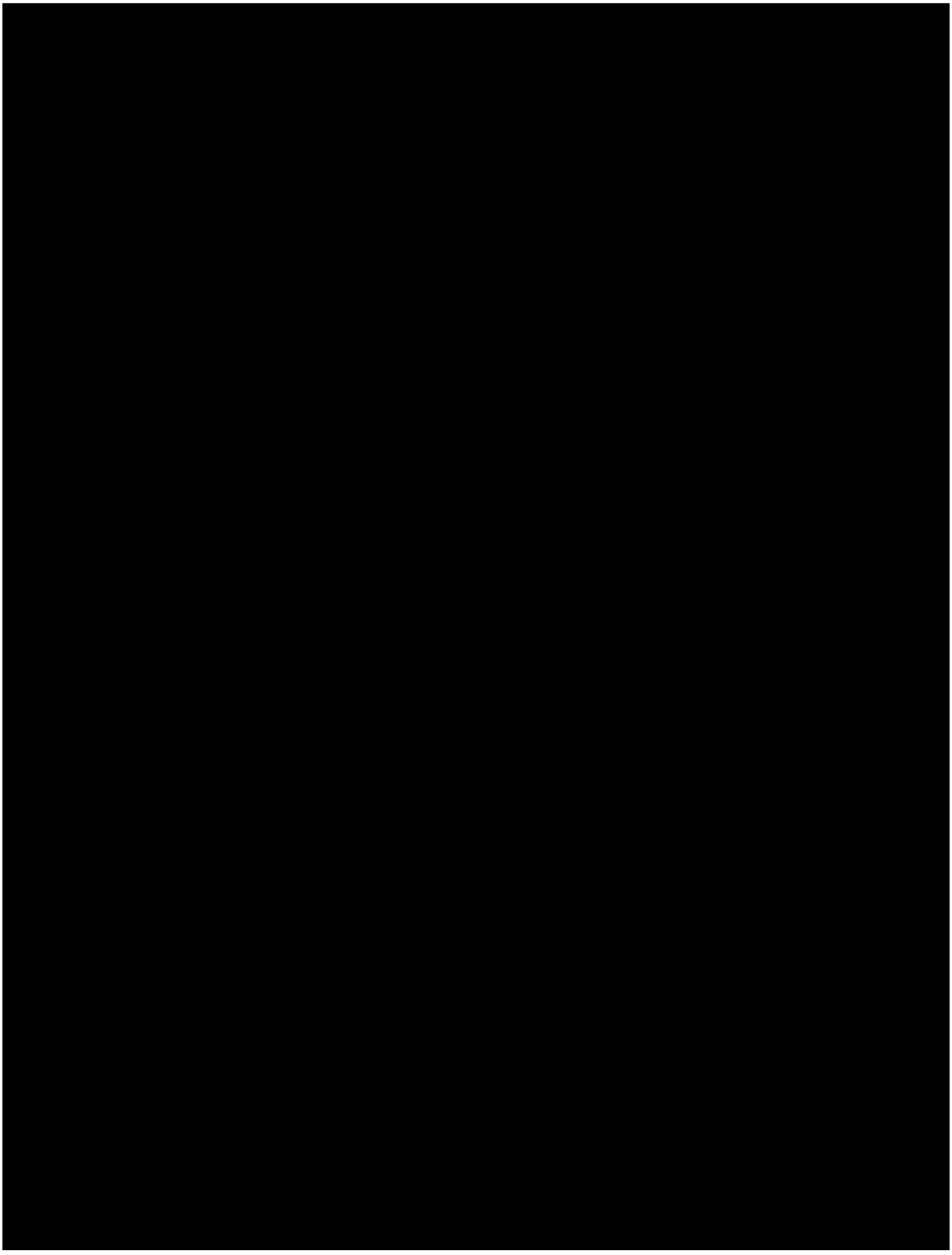




Complete the signature section at the bottom of each page and fax the form to Amgen.







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:** _____

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Appendix E. Correct Answer Document

Removed to allow unbiased data