Survey of Oncology Practitioners Prescribing XGEVA® in Europe to Evaluate Their Knowledge of XGEVA® Summary of Product Characteristics Pertaining to Osteonecrosis of the Jaw

Amgen Protocol Number 20110102

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Confidentiality Notice

Protocol Synopsis

Title: Survey of Oncology Practitioners Prescribing **XGEVA®** in Europe to Evaluate Their Knowledge of **XGEVA®** Summary of Product Characteristics Pertaining to Osteonecrosis of the Jaw

Study Phase: Phase 4, Post-Authorisation Observational Study

Indication: XGEVA ® (denosumab 120 mg every 4 weeks [Q4W]) is indicated for the prevention of skeletal related events (SREs) in adults with bone metastases from solid tumours

Primary Objective:
To survey oncology practitioners prescribing **XGEVA®** in Europe to evaluate their knowledge of the XGEVA Summary of Product Characteristics (SPC) pertaining to osteonecrosis of the jaw (ONJ). Statements in the XGEVA SPC include:

- ONJ has been reported in patients treated with denosumab
- A dental examination with appropriate preventive dentistry should be considered prior to treatment with XGEVA in patients with active dental and jaw conditions
- Patients should avoid invasive dental procedures, if possible, while on treatment with XGEVA
- Good oral hygiene practices should be maintained during treatment with XGEVA™
- Patients who are suspected of having or who develop ONJ while on XGEVA therapy should receive care by a dentist or oral surgeon
- Extensive dental surgery to treat ONJ may exacerbate the condition

Hypotheses: This study is descriptive in nature and does not involve hypothesis testing. This study will estimate the proportion of XGEVA prescribing oncology practitioners who are aware of the statements in the SPC.

Study Design: Two cross-sectional surveys of oncology practitioners prescribing XGEVA

Study Endpoints:
The endpoints of this study will be addressed using the following statistics:

- Proportion of participating oncology practitioners prescribing XGEVA who are aware of the SPC statements pertaining to ONJ (each question pertaining to a SPC statement will be assessed separately at the end of each survey round)
- XGEVA**The first round of survey will be conducted 12 to 18 months after XGEVA becomes commercially available in the participating countries**
- **The second round of surveys will be 24 to 30 months after XGEVA becomes commercially available in the participating countries**

Sample Size:
A total of 210 oncology practitioners who agree to participate will be included in each cross-sectional survey and a total of 420 oncology practitioners who agree to participate will be included in both cross-sectional surveys, which will be analyzed together. Based on the sample size of 420 oncology practitioners in both surveys, the 95% confidence interval is ± 4% around a proportion of 80% and ± 3% around a proportion of 90%. Based on the sample size of 210 oncology practitioners in each survey, the 95% confidence interval is ± 5% around a proportion of 80% and ± 4% around a proportion of 90%.

Summary of Subject Eligibility Criteria:
Oncology practitioners satisfying all of the following eligibility criteria are eligible to be enrolled in the survey:

- must be a practicing oncology specialist
- has to have treated at least 5 new or continuing adult patients with bone metastases from solid tumours in the last quarter
- must not have participated in a previous survey round
- must have prescribed XGEVA within the last 12 months

Procedures:

The survey will be conducted for 2 rounds.

The first survey round will be collected 12 to 18 months after XGEVA becomes commercially available in the participating countries. The second round will be collected 24 to 30 months after XGEVA becomes commercially available in the participating countries.

150 oncology practitioners from across but not limited to the 5 largest European countries by population (France, Germany, Italy, Spain and the U.K.) and 60 oncology practitioners from 4 Nordic countries (Denmark, Finland, Norway and Sweden) will be sampled per survey round. The Nordic countries are included to provide background information on physician knowledge for Amgen Study 20101363 of ONJ in patients receiving XGEVA in Denmark, **Norway** and Sweden.

In each round of survey, potential participating oncology practitioners will be sampled randomly from each country's sampling list and will be contacted by mail, telephone, fax **or** email. During the initial contact, the oncology practitioners will be assessed for their eligibility to participate in the study using a standardized set of screening questions.

The initial contact and screening of potential participating oncology practitioners will continue until a total of 210 eligible oncology practitioners agree to participate. **For the 5 largest European countries by population, it is intended that 30 oncology practitioners will be surveyed per country per survey round. If this sample size cannot be achieved, oncology practitioners from another country in that region will be surveyed to achieve the pre-specified regional sample size of 150 per survey round. Oncology practitioners from the Nordic countries will be surveyed to achieve a regional sample size of 60 per survey round. For all participating countries, the number of surveys collected in each country in the second survey round will, where possible, equate to the number of surveys collected in each country in the first survey round.**

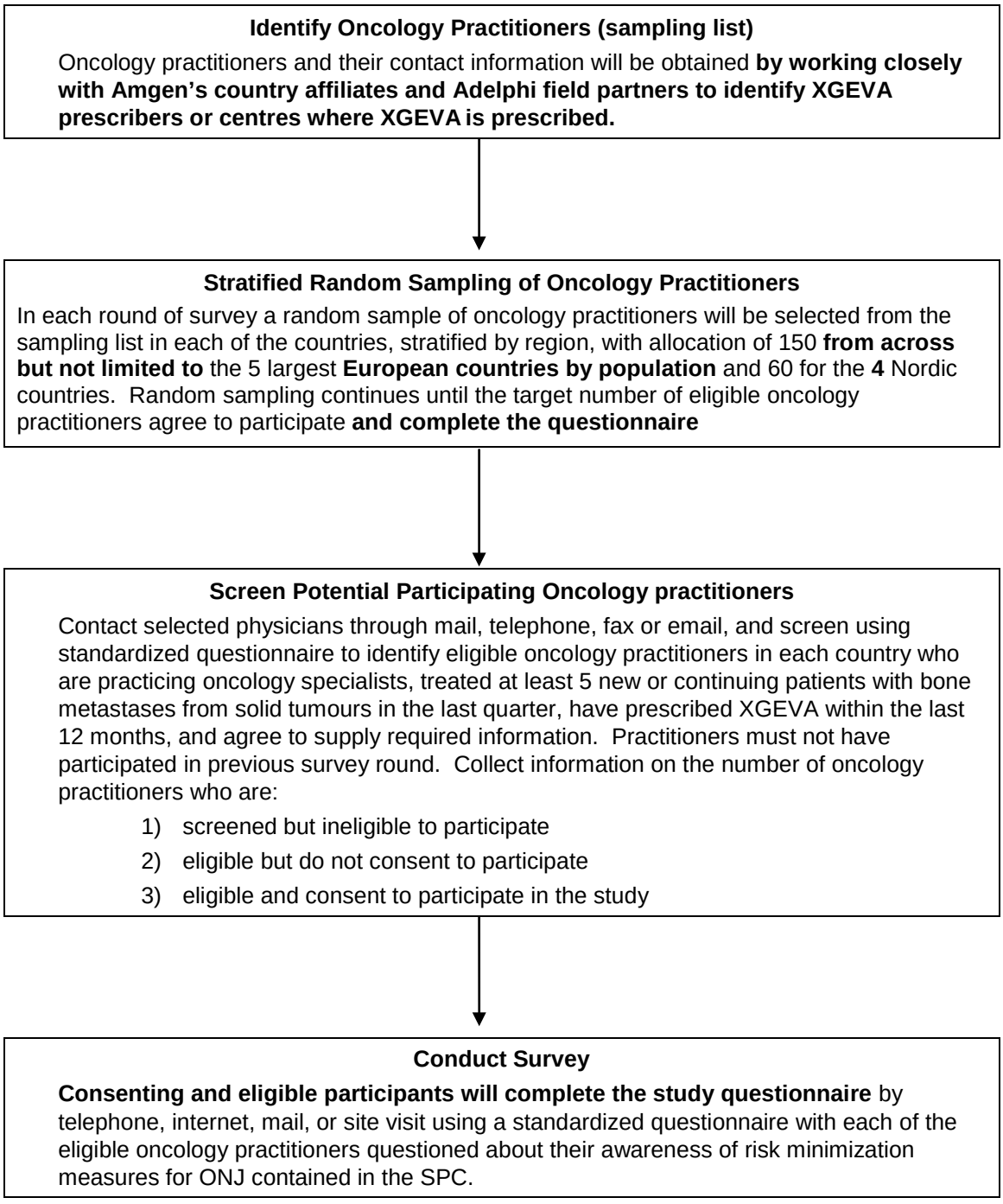
Consenting and eligible participants will complete the study questionnaire by telephone, internet, mail, or site visit using a standardized questionnaire with each of the eligible oncology practitioners questioned about their awareness of risk minimization measures for ONJ contained in the SPC.

Statistical Considerations:

The data analysis is descriptive in nature. The descriptive statistics for all study endpoints will be calculated both overall and stratified by region (EU and Nordic countries). Additional process measures for participation rates will also be calculated including:

- Proportion of oncology practitioners contacted who are eligible to participate in the study
- Proportion of eligible oncology practitioners contacted who agree to participate

Study Design and Treatment Schema



Study Glossary

Abbreviation or Term	Definition/Explanation
ADR	Adverse Drug Reaction
AE	Adverse Event
Cegedim	Public company specializing in healthcare with extensive databases of healthcare practitioners
CHMP	Committee for Medicinal Products for Human Use
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
EU	European Union
ID	Identification
MAH	Marketing Authorization Holder
ONJ	Osteonecrosis of the jaw
Oncology Practitioner/Specialist	**Practicing physician treating cancer patients**
Q4W	Every 4 weeks
RMP	Risk Management Plan
PSUR	Periodic Safety Update Report
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SPC	Summary of Product Characteristics
SOP	Standard Operating Procedures
SREs	Skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone)

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1. OBJECTIVE

Primary Objective: To survey oncology practitioners prescribing XGEVA® in Europe to evaluate their knowledge of the XGEVA SPC pertaining to osteonecrosis of the jaw (ONJ).

2. BACKGROUND AND RATIONALE

2.1 Indication for XGEVA®

Denosumab is a fully human monoclonal antibody of the IgG_2 subclass that binds with high affinity (Kd 3 x 10^{-12} M) and specificity to the soluble and cell membrane-bound forms of human RANKL. Denosumab binding to RANKL prevents RANK activation and inhibits the formation, activation, and survival of osteoclasts. As a consequence, bone resorption and cancer-induced bone destruction are reduced. As a result of its unique and specific mechanism of action, denosumab has been investigated for use in patients with metastases to bone to prevent the occurrence of skeletal-related events (SREs).

Efficacy results from three phase 3 pivotal studies (20050136, 20050244, and 20050103) showed a consistent treatment effect of denosumab across tumour types for reduction in the occurrence of SREs. Specifically, the results for all SRE-related endpoints, whether from the individual studies or the integrated analysis, demonstrated either superiority or favorable efficacy for denosumab compared with the current standard of care, zoledronic acid (Zometa®). In a combined analysis of the 3 pivotal clinical trials for XGEVA™, the 1-year cumulative incidences of adjudicated ONJ were 0.8% and 0.5% for patients treated with denosumab and zoledronic acid, respectively. The respective cumulative incidences were 1.8% and 1.0% at 2 years and 1.8% and 1.3% at 3 years. In these studies, a history of either tooth extraction, poor oral hygiene (eg, periodontal disease, gingivitis), or use of a dental appliance was common in subjects who developed ONJ. The association of ONJ with other risk factors common among the advanced cancer population, such as exposure to antiangiogenics and corticosteroids, was much less pronounced, and no notable association was evident with prior use of bisphosphonates or chemotherapy (data on file). The rates of ONJ seen in these studies were within the range of published estimates for advanced cancer populations treated with bisphosphonates (Migliorati et al, 2010; Ruggiero et al, 2009; Wimalawansa, 2008; Woo et al, 2006).

2.2 Rationale for the Survey of Oncology Practitioners

ONJ is an adverse effect of antiresorptive therapy that is well-recognized in patients with advanced cancer. Risk factors for ONJ include tooth extraction and poor oral hygiene

(eg periodontal disease). Risk minimization measures have been successful in specific studies (Dimopoulos et al, 2009; Ripamonti et al, 2009) and are recommended (American Association of Oral and Maxillofacial Surgeons, 2009).

Detailed information regarding this well-recognized risk is specified in the Summary of Product Characteristics (SPC). Amgen considers that the clear statements in the SPC, which focus on preventive dentistry and conservative dental management during treatment with denosumab, are the most important mechanisms for minimizing the risk for ONJ. Statements in the denosumab SPC include:

- ONJ has been reported in patients treated with denosumab
- A dental examination with appropriate preventive dentistry should be considered prior to treatment with XGEVA in patients with active dental and jaw conditions
- Patients should avoid invasive dental procedures, if possible, while on treatment with XGEVA
- Good oral hygiene practices should be maintained during treatment with XGEVA™
- Patients who are suspected of having or who develop ONJ while on XGEVA therapy should receive care by a dentist or oral surgeon
- Extensive dental surgery to treat ONJ may exacerbate the condition

The study objective is to measure the knowledge of oncology practitioners prescribing XGEVA regarding the content pertaining to ONJ in the SPC.

2.3 Study Hypothesis

This study is descriptive in nature and does not involve formal hypothesis testing. However, the study will estimate the proportion of oncology practitioners prescribing XGEVA who correctly identify true statements pertaining to ONJ in the SPC (proportion calculated for each individual statement) and the associated 2-sided 95% confidence interval.

3. STUDY DESIGN

This is a multiple cross-sectional survey study of practicing oncology practitioners **prescribing XGEVA in Europe from across but not limited to** the 5 largest European countries by population (including France, Germany, Italy, Spain and the U.K.) and **4** Nordic countries(Denmark, **Finland, Norway and** Sweden). The survey will be conducted **in two rounds. The two survey rounds will be conducted 12 to 18 months and 24 to 30 months after XGEVA becomes commercially available in the participating countries.**

Before each survey round is conducted in the participating countries, a sampling list will be derived from lists of oncology practitioners (and their contact information). These lists will be assembled by working closely with Amgen's country affiliates and Adelphi field partners to identify XGEVA prescribers.

In each round of the survey, potential participating oncology practitioners will be selected by stratified random sampling (by country) and contacted by mail, telephone, fax **or** email. During the initial contact of each round of survey, the oncology practitioners will be introduced to the background, objective, and plan of the study and their eligibility to participate in the study will be assessed using standardized screening questions. The initial contact and screening of potential participating oncology practitioners will continue until a total of 210 eligible and consenting oncology practitioners are identified **per survey round**. The number of oncology practitioners contacted but not enrolled in the study including the number of non-respondents, the number of screened but ineligible oncology practitioners, and the number of eligible but nonconsenting oncology practitioners will be recorded.

The eligible oncology practitioners **will complete a standardized questionnaire that may be completed by telephone, internet, mail, or site visit** to **collect information about** their awareness or knowledge of the risk minimization measures for ONJ contained in the SPC.

A sample of 150 participants from including but not limited to the 5 largest European countries by populationand a sample of 60 participants from 4 Nordic countries will be sampled randomly from the country-level master list of prescribers per survey round. There are 2 purposes for this stratification: 1) to allow an adequate number (N = 150) for interpretation by regulatory authorities of the results for oncology practitioners prescribing XGEVA in the EU in terms of the width of the 95% confidence interval; and 2) to obtain an adequate sample (N = 60) for the Nordic countries in terms of the confidence interval with the latter results providing the background of physician knowledge for the Amgen study of ONJ incidence in patients receiving XGEVA in Denmark**, Norway** and Sweden (Amgen Study 20101363).
See Section 4 for associated 95% confidence intervals with different proportions.

For the 5 largest European countries by population, it is intended that 30 oncology practitioners will be surveyed per country per survey round. If this sample size cannot be achieved, oncology practitioners from another country in that region will be surveyed to achieve a regional sample size of 150 per survey round.

Oncology practitioners from the Nordic countries will be surveyed to achieve a regional sample size of 60 per survey round. For all countires, the number of surveys collected in each country in the second survey round will, where possible, equate to the number of surveys collected in each country in the first survey round.

3.1 Source Population and Selection of Participants

The study population consists of oncology practitioners enrolled from the participating countries. To identify these oncology practitioners, **before the beginning of each survey round** contact information of oncology practitioners will be obtained from **a master list of eligible respondents assembled by working with Amgen country affiliates and Adelphi field partners to identify XGEVA prescribers or centers where XGEVA is prescribed** . Potential participating oncology practitioners will be sampled randomly from all identified oncology practitioners in each country to ensure the sample is representative of all oncology practitioners who treat patients regularly in each country. In each round of the survey, the study staff will contact the sample of identified oncology practitioners through mail, telephone, fax **or** email to introduce the study and to assess eligibility of each contacted person to participate in the survey. **Participants who took part in the first survey round will not be included in the second round.** To ensure that the same oncology practitioner does not participate in the study twice, eligible oncology practitioners who participated in the first round of survey will not be included in the sampling for the second survey round. To ensure the survey results represent practicing oncology practitioners who prescribe XGEVA, participants must satisfy all of the following eligibility criteria to be enrolled in the survey:

- must be a practicing oncology specialist
- has to have treated at least 5 new or continuing patients with bone metastases from solid tumours in the last quarter
- must not have participated in a previous survey round
- must have prescribed XGEVA within the last 12 months

The initial contact and screening of potential participating oncology practitioners will continue until a total of 210 eligible and consenting oncology practitioners are identified in each round. If there is no response to the initial contact, up to 5 additional contact attempts will be made to enhance participation in non-responders (a total of 6 attempts). These 6 attempts would consist of at least 2 different modalities of the following: email, telephone call, and, potentially, other contact attempts by fax **or** email. The number of

oncology practitioners contacted but not enrolled in the study, including the number of nonrespondents, the number of screened but ineligible oncology practitioners, and the number of eligible but nonconsenting oncology practitioners will be recorded. The same process of sampling, contact, and screening of oncology practitioners will be conducted at approximately12 **to 18 months and 24 to 30** months after commercial availability of XGEVA. To increase the participation rate, provided it is allowed by local legislation or guidelines, each eligible participant may be paid fair market value to compensate for the time they spend on the survey.

3.2 Data Collection

Each round of survey will be conducted using the standard study questionnaire (Appendix B). The survey rounds will be conducted 12 to 18 months (for survey round 1) and 24 to 30 months (for survey round 2) after commercial availability of XGEVA in each country. A minimum gap of 6 months will be maintained between survey rounds.

3.3 Training of Interviewers

To ensure consistent procedures and data collection across all study participants, study operation manuals for field staff will be developed and used to train all study staff. Each study staff member will need to complete the required training before conducting the **study data collection**.

3.4 Data Collection Instruments

The process and materials for screening oncology practitioners for eligibility and **study data collection** with a standard questionnaire will be developed based on readability tests and expert review which may be conducted as soon as the SPC is available in the local language. Since this is a multi-national study, the questionnaire will be carefully translated to ensure that the content and the way of asking questions are consistent across the countries. The translated questionnaire will be checked for consistency with the local SPC with a readability test in the local language. To ensure all questions are well targeted and correctly understood, test **questionnaires** will be **completed** with the translated version of the questionnaire for each country prior to the first round of the survey by review with 2 oncology practitioners per country. The questions will be reviewed and may be modified as needed depending on the outcome of the test **questionnaires**. Results from the readability tests and practitioner reviews will not be included in the final analysis. **The questionnaire is attached in Appendix B to this protocol.**

3.5 Follow-up Procedures

This study involves 2 cross-sectional physician surveys and no follow-up will be conducted.

3.6 Potential Sources of Bias in Study Design

Oncology practitioners eligible to participate in the study may decline to participate for various reasons; consequently, response from the participating oncology practitioners may not be generalisable to all eligible oncology practitioners in each country. For example, oncology practitioners who are involved in administrative, research, or teaching activities may be less likely to participate because of their busy schedule.

The number of surveys collected in each country in the second survey round will, where possible, equate to the number of surveys collected in each country in the first survey round.

Questions involving behavior such as number of patients treated, stated prescribing of XGEVA, and stated instructions to patients will not be independently verified.

4. STUDY SIZE

A total of 210 oncology practitioners, 150 from **across but not limited to** the 5 largest **European** countries **by population (France, Germany, Italy, Spain and the U.K.)** and 60 **oncology practitioners** from **the 4 participating** Nordic countries (Denmark**, Finland, Norway** and Sweden) who agree to participate will be included in each cross-sectional survey and a total of 420 oncology practitioners who agree to participate will be included in the 2 cross-sectional surveys combined. Based on the sample size of 1 or 2 rounds of the survey, the half-width of the 95% confidence intervals around a range of proportions from 50% to 90% is shown in Table 1.

Table 1. Half-width of 95% Confidence Intervals for Different Proportions by Size of Survey Round and Number of Surveys

		Half-width of 95% Confidence Interval	
Round Size	Proportion	1 Survey **Round**	**2 Survey Rounds**
150	0.5	0.08	0.06
150	0.6	0.08	0.06
150	0.7	0.07	0.05
150	0.8	0.06	0.05
150	0.9	0.05	0.03
60	0.5	0.13	0.09
60	0.6	0.12	0.09
60	0.7	0.12	0.08
60	0.8	0.10	0.07
60	0.9	0.08	0.05
210	0.5	0.07	0.05
210	0.6	0.07	0.05
210	0.7	0.06	0.04
210	0.8	0.05	0.04
210	0.9	0.04	0.03

5. STATISTICAL ANALYSIS

No formal hypothesis testing will be conducted. The study endpoints will be addressed using descriptive statistics, including:

- Proportion of participating oncology practitioners prescribing XGEVA who are aware of the SPC statements pertaining to ONJ (each question pertaining to a SPC statement will be assessed separately at the end of each survey round)
- The above endpoints in **approximately** month 12 and month 24 after commercial availability of XGEVA in the respective countries

Note that different countries will have different start times and different sets of oncology practitioners will be sampled in each of the survey sampling rounds.

Questions not answered will be considered as incorrect answers and included in the denominators. Standard errors will be estimated based on the normal approximation to the binomial distribution (using the central limit theorem). Two-sided 95% confidence intervals will be estimated as the estimated proportion ± 1.96 multiplied by the estimated standard error.

Results will be presented by the following:

- Each survey round individually and the 2 surveys combined cumulative total after the second round
- Stratification of the above by the 2 regions: Nordic countries (Denmark, Finalnd, Norway and Sweden) versus the 5 largest European countries by population size

Additional process measures for participation rates will also be calculated including 2-sided 95% confidence intervals for the following:

- Proportion of oncology practitioners contacted who are eligible to participate
- Proportion of eligible oncology practitioners contacted who agree to participate

6. STUDY LIMITATIONS

Limitations of this study include the potential lack of generalisability to all oncology practitioners who prescribe XGEVA due to the selection processes. Two aspects of the study design introduce variability into the sampling scheme and interpretation:

1) The choice to include actual prescribers of XGEVA rather than a fixed population of potential prescribers may cause the 2 survey rounds to differ in the source population, as the group of actual prescribers is expected to change over time; thus, the 2 populations may not be strictly comparable. The choice to include only actual prescribers also constrains the opportunity to establish a baseline level of knowledge of measures to prevent ONJ.
2) The random sampling list may identify oncologists with different levels of experience or from different types of oncology facility, between different survey rounds. As a result of these potential sources of bias, the characteristics of oncologists who participate in each survey round may differ, which may mean that inter-round differences in response rates to survey questions could be associated with the differences between the oncologists participating in each survey round.

Other limitations have been presented in Section 3.6, Potential Sources of Bias in Study Design.

7. ETHICAL AND REGULATORY OBLIGATIONS

7.1 Protection of Human Subjects

Approval will be determined by local ethics committee, as needed, to conduct the survey in each country. Data from all interviews will be anonymised. Study staff will be instructed not to divulge any personal information relating to any of the interviewees. Any identifying information revealed during the interview will be removed from the interview transcript.

8. SAFETY DATA COLLECTION, RECORDING AND REPORTING

8.1 Definition of Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product(s) and which does not necessarily have to have a causal relationship with this treatment.

An AE 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 AE includes:

- Worsening of a pre-existing condition
- Events occurring from a medication error or overdose of a product(s), whether accidental or intentional
- Events occurring from abuse of a product(s)
- Events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms)
- Any lack or loss of intended effect of the product(s)

8.1.1 Adverse Drug Reactions (ADRs)

AEs that are considered related to the Amgen product(s) are classified as adverse drug reactions (ADRs).

It is the Investigator's responsibility to evaluate if an event is related to an Amgen product prior to reporting the event to Amgen.

8.1.2 Definition of Serious Adverse Events

A serious adverse event (SAE) is any AE as defined above that also:

- is fatal
- is life threatening (places the patient at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an "other significant medical hazard" that does not meet any of the above criteria

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

"Other significant medical hazards" refer to important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the

patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

8.1.2.1 Serious Adverse Drug Reactions (SADRs)

SAEs that are considered related to the Amgen product(s) are classified as serious adverse drug reactions (SADRs).

It is the Investigator's responsibility to evaluate if an event is related to an Amgen product prior to reporting the event to Amgen.

8.1.3 Definition of Other Safety Findings

Other Safety Findings include:

- Medication errors, overdose, misuse, or abuse, whether accidental or intentional, involving an Amgen product, regardless of whether associated with an AE and/or SAEs
- Pregnancy and lactation exposure regardless of whether associated with an AE or and/or SAEs
- Transmission of infectious agents regardless of whether associated with an AE and/or SAEs
- Reports of uses outside the terms for authorized use of the product including off label use when associated with an AE and/or SAEs

8.1.4 Definition of Product Complaints

Product Complaints include any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product or device after it is released for distribution. This includes all components distributed with the product(s) such as packaging, product containers, delivery system, labeling, inserts, etc.

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

- Appearance (eg, broken, cracks, color, particles, odor)
- Labeling (eg, missing, torn, smudged)
- Durability (eg, stability issues)
- Open packaging
- Device damage (eg, pre-filled syringe with bent needle)

- Inability of customer to understand product labeling
- Inability of customer to deliver the product successfully, including partial or incomplete delivery (eg, defective delivery system [syringe])

8.2 Reportable Events and Reporting Timeframes

The vendor is responsible for ensuring that all AEs, product complaints and other safety findings for Amgen products reported by HCPs and/or consumers are submitted to Amgen via the supplied Amgen Safety Reporting Forms. See Appendix A for a sample Report Form.

Refer to Table 2 for the reporting timeframes for reportable events.

The vendor is to provide event listings to Amgen for purposes of reconciliation per the contractual agreement.

Table 2. Reporting Timeframes for Reportable Events

Report Type	Description	Reporting Timeframe
SAE	Initial or follow-up for SAEs	Within 1 business day of vendor awareness
Product complaints	Initial or follow-up of all product complaints	Within 1 business day of vendor awareness
Pregnancy and/or Lactation	• Initial or follow-up for all pregnancies or lactation occurring in females while taking Amgen product(s) and/or • Initial or follow-up for all pregnancies or lactation occurring in female partners of males taking Amgen product(s)	Within 1 business day of vendor awareness
Other / Non serious AE	Initial or follow-up for AE not meeting serious criteria	Within 30 days of awareness

9. DATA MANAGEMENT AND QUALITY CONTROL PROCEDURES

All electronic data files will be de-identified and stored in password-protected computers. Response data from the interview for each participating oncologist will be linked through an assigned unique study ID. No patient-level personal or confidential medical information will be collected during this study.

10. COMMUNICATION OF STUDY RESULTS

Interim reports summarizing results from the survey in approximately **18** and **30** months after XGEVA becomes commercially available will be provided to the EMA in the next Periodic Safety Update Report (PSUR) after the analysis and summarization of results are completed. The final report will include data from the current survey and cumulative data from the previous survey. Aggregate results may also be presented at a clinical meeting and/or submitted for publication in a medical journal.

11. REFERENCES

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12. APPENDICES

Appendix A. Amgen Safety Reporting Form

Project ID: 20110102	AMGEN	Safety Reporting Form Primary Data Collection	Date of Report:
		Fax reports to: UK +44 20 7136 1046	

1. Indicate event type: ☐ AE/Other safety finding ☐ AE/Other safety finding with Product Complaint ☐ Product Complaint only

2. Vendor Contact Details

name	phone	fax
address		
city	state/province	
postal code	country	

3. Reporter ID

Name or ID	phone	fax
address		
city	state/province	
postal code	country	

4. HCP Contact Details (if other than reporter)

name		
country		
address		
city	state/province	postal code
phone	fax	

5. Patient

Initials (optional)	Sex	Age (at time of event)	Was consent obtained to follow-up with HCP?
	☐ F ☐ M		☐ Yes ☐ No
Weight: ☐ lbs ☐ kg	Height: ☐ in ☐ cm	Race	Is patient also reporter? ☐ Yes ☐ No

6. Medical History (include primary diagnosis)

7. Suspect Product Information (include dosing details)

Product: _____

Indication: _____

	Start Date (day month year)	Stop Date (day month year)	Dose	Route	Freq

Pregnant? ☐ Yes ☐ No Lactating? ☐ Yes ☐ No

Allergy: _____

Prefilled Syringe? ☐ Yes ☐ No

Other Device _____

Lot # _____ ☐ Unknown

Vial size

8. AE, other safety finding, or product complaint information | **HCP ONLY**

Finding (List main event first; one event per line)	Onset Date (day month year)	Resolved Date (If patient died, list date of death) Cause of Death: _____ (provide autopsy report) (day month year)	Hospitalization: Hospitalized? ☐ Yes ☐ No; Hospitalization Prolonged? ☐ Yes ☐ No; Admitting dx _____ (provide discharge summary); Date Admitted (day month year)	Date Discharged (day month year)	Serious Criteria (1=persistent or significant disability/ incapacity; 2=congenital anomaly/ birth defect; 3=significant medical hazard)	Action Taken (1=none; 2=dose reduced; 3=dose increased; 4=drug withdrawn; 5=Drug rechallenge (state outcome))	Outcome (1=resolved; 2=resolved w/ sequelae; 3=resolving; 4=event ongoing; 5=died of event)	Severity (1=mild; 2=moderate; 3=severe; 4=life-threatening; 5=fatal)	Relationship to Product/ Device: Is there a reasonable possibility that this event may have been caused by the Product / Device? Product	Device
									Y N	Y N
									Y N	Y N
									Y N	Y N

9. Description: chronological summary of symptoms or product complaint from above (signs, diagnosis, treatment, concomitant medications including those used to treat event.)

Reporter Signature: _____ Page 1 of _____

The data provided by you will be transferred as a report to Global Safety at Amgen Inc (USA) and will be exclusively used for safety and quality purposes
For vendor surveys of Health Care Professionals

FORM-067756 Ver. #: 1.0 Effective date: 20-Aug-2012 Page 1 of 1 *ADR Form Created: DD-MMM-YYYY*

Appendix B. Questionnaire for the Assessment of Physician's Knowledge of the SPC

A. Introduction

We are contacting you as a potential participant for a survey study regarding the current treatment recommendations for use of denosumab, trade name XGEVA® indicated for prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours. If you are eligible and complete the survey, you may be reimbursed for your time. The Survey will take approximately 15 minutes.

We would like to reassure you that any personal information you provide is highly confidential. The transcript of this interview will not contain your name, your address, your email address or your telephone number. All collected information will strictly be used to address the pre-specified objective of this study regarding XGEVA® (denosumab) and treatment of bone metastases from solid tumours.

As the first step, we are going to ask you a few questions to assess your eligibility to participate in this study.

B. Screening Questions

a. Are you a practicing oncology specialist? (Yes/No). (If response is "No", **potential participant is screen failed;** if answer to question a is "YES" ask question b.)

b. How many patients, new or continuing, with bone metastases from solid tumours did you see in the last 3 months? (If answer to question b is less than 5, **potential participant is screen failed;** if answer to question b is 5 or greater, ask question c.)

c. Have you prescribed XGEVA® (denosumab), for treatment of bone metastases from solid tumours in the previous 12 months? (If response is "No", **potential participant is screen failed;** if answer to question c is "YES" ask question d.)

d. Will you agree to participate in this survey study and provide information about your knowledge of the safe use of XGEVA® (denosumab)? (If response is "No", **potential participant is screen failed;** if answer to question a is "YES", continue to questionnaire.)

Thank you for agreeing to participate. Throughout the questionnaire, please ensure that your responses are specific and limited to your understanding of what is described in the summary of product characteristics for XGEVA® (denosumab), particularly in relation to ONJ (osteonecrosis of the jaw).

Instructions: For the following multiple choice questions, select only 1 of the choices. Only one of the 3 choices is correct regarding **the summary of XGEVA® (denosumab) product recommendations. (Note: ONJ is the abbreviation used for osteonecrosis of the jaw).**

C. Survey Questions

1) Which one of the following statements is correct regarding osteonecrosis of the jaw (ONJ)?

   a) XGEVA® (denosumab) is contraindicated in patients who have existing dental implants.

   b) ONJ has not been reported in patients treated with XGEVA® (denosumab) but is a potential risk as ONJ has been observed in patients treated with bisphosphonates which also have an antiresorptive effect on bone

   c) ONJ has been reported in patients treated with XGEVA® (denosumab)

2) Which one of the following statements is correct regarding patients who have concomitant risk factors for ONJ?

   a) Duration of therapy with XGEVA® (denosumab) is recommended to be no more than 12 months.

   b) A dental examination with appropriate preventive dentistry should be considered prior to treatment with XGEVA® (denosumab) in patients with active dental and jaw conditions

   c) Antibiotic mouth rinses are recommended for patients during treatment with XGEVA® (denosumab)

3) Which one of the following statements is correct regarding dental procedures?

   a) Patients should avoid invasive dental procedures, if possible, during treatment with XGEVA® (denosumab)

   b) Patients should avoid invasive dental procedures, if possible, during treatment with XGEVA® (denosumab) and for the following 12 months after discontinuation of XGEVA® (denosumab)

   c) Antibiotics are recommended prophylactically in patients receiving treatment with XGEVA® (denosumab) who are undergoing dental procedures

4) Which one of the following statements is correct regarding oral hygiene practices?

   a) Antibiotic mouth rinses are recommended for patients who are not able to maintain good oral hygiene practices during treatment with XGEVA® (denosumab)

   b) Good oral hygiene practices should be maintained during treatment with XGEVA® (denosumab)

   c) Good oral hygiene practices are sufficient to treat most cases of ONJ that develop during treatment with XGEVA® (denosumab)

5) Which one of the following statements is correct regarding patients who are suspected of having or who develop ONJ while on therapy with XGEVA® (denosumab)?

   a) Patients should receive antibiotics covering methicillin-resistant Staphylococcus aureus

   b) Patients should receive care by a dentist or oral surgeon.

   c) In all cases of ONJ, patients should receive surgery to debride the site of ONJ back to viable bone

6) Which one of the following statements is correct regarding surgery to treat ONJ?

   a) ONJ may require extensive dental surgery to expose viable bone to allow healing.

   b) In most cases of ONJ, surgery should be directed at the underlying cancer metastatic to the jaw.

   c) Extensive dental surgery to treat ONJ may exacerbate the condition.

This completes the interview. Thank you for your time.

Amendment 3

Protocol Title: Survey of Oncology Practitioners Prescribing XGEVA® in Europe to Evaluate Their Knowledge of XGEVA® Summary of Product Characteristics Pertaining to Osteonecrosis of the Jaw

Amgen Protocol Number 20110102

Amendment 3 Date: 16 July 2013

Rationale:

The 20110102 protocol is being amended to allow Amgen to meet the pre-specified sample sizes of 150 XGEVA® prescribers from the 5 largest European countries by population and 60 XGEVA® prescribers from the Nordic region, in each of the 2 rounds of survey. In the Nordic region the number of participating countries has been increased from 2 to 4 with the inclusion of Finland and Norway. In the European region, the changes allow oncology practitioners from another country from that region to be surveyed if a sample size of 30 cannot be achieved in any of the participating countries. These changes stem from a need to adapt to the real-world economic developments and associated reimbursement rulings that drive physician prescribing behavior in Europe. Further details on data sources, sampling strategy and measures to reduce bias are also included.

Description of Changes

Section: All

Replace:

XGEVA™

With:

XGEVA®

Section: Key Sponsor Contact

Replace:

Scott Stryker, MD, MPH, DrPH
Amgen Centre for Observational Studies
Tel: 1 650-244-3622

With:

Alexander Liede, PhD
Amgen Centre for Observational Studies
Tel: 1 650-244-2418

Section: Protocol Synopsis – Study Phase

Replace:

Not applicable

With:

Phase 4, Post-Authorisation Observational Study

Section: Protocol Synopsis – Study Endpoints

Replace:

The above endpoints in the 12th month and 24th month after XGEVA™ becomes commercially available in the respective countries

With:

- The first round of survey will be conducted 12 to 18 months after XGEVA becomes commercially available in the participating countries
- The second round of surveys will be 24 to 30 months after XGEVA becomes commercially available in the participating countries

Section: Protocol Synopsis – Procedures

Replace:

The survey will be conducted for 2 rounds starting approximately 12 and 24 months after XGEVA™ becomes commercially available in each country. Before each survey round, the sampling list will be derived from lists of oncology practitioners (and their contact information). These lists are to be collected from the European Society of Medical Oncology (ESMO), from major cancer centers, oncology clinics, Cegedim (a commercial source), and other sources in 5 large countries of Europe, including France, Germany, Italy, Spain, and the UK, and 2 Nordic countries, Denmark and Sweden.

With:

The survey will be conducted for 2 rounds. The first survey round will be 12 to 18 months after XGEVA becomes commercially available in the participating countries. The second round will be collected 24 to 30 months after XGEVA becomes commercially available in the participating countries.

150 oncology practitioners from across but not limited to the 5 largest European countries by population (France, Germany, Italy, Spain and the U.K.) and 60 oncology practitioners from 4 Nordic countries (Denmark, Finland, Norway and Sweden) will be sampled per survey round.

Replace:

The latter 2 Nordic countries

With:

The Nordic countries

Replace:

Patients receiving XGEVA in Denmark and Sweden.

With:

Patients receiving XGEVA in Denmark, Norway and Sweden.

Replace:

Will be contacted by mail, telephone, fax, email, or a site visit.

With:

Will be contacted by mail, telephone, fax or email.

Replace:

In the 7 countries. The number of oncology practitioners recruited in each country will be stratified by region with allocation of 150 for the 5 large EU countries and 60 for the 2 Nordic countries.

With:

For the 5 largest European countries by population it is intended that 30 oncology practitioners will be surveyed per country per survey round. If this sample size cannot be achieved, oncology practitioners from another country in that region will be surveyed to achieve the pre-specified regional sample size of 150 per survey round. Oncology practitioners from the Nordic countries will be surveyed to achieve a regional sample size of 60 per survey round. For all participating countries, the number of surveys collected in each country in the second survey round will, where possible, equate to the number of surveys collected in each country in the first survey round.

Replace:

Interviews will be conducted

With:

Consenting and eligible participants will complete the study questionnaire

Section: Protocol Synopsis – Study Design and Treatment Schema

Replace:

Identify Oncology Practitioners (sampling list)

Oncology practitioners and their contact information will be obtained from ESMO, major oncology clinics, cancer centers, Cegedim (a commercial source), and other sources in France, Germany, Italy, Spain, the UK, Denmark, and Sweden

With:

Identify Oncology Practitioners (sampling list)

Oncology practitioners and their contact information will be obtained by working closely with Amgen's country affiliates and Adelphi field partners to identify XGEVA prescribers or centres where XGEVA is prescribed

Replace:

Stratified Random Sampling of Oncology Practitioners

In each round of survey in approximately 12 and 24 months after commercial availability for each country, a random sample of 30 oncology practitioners will be selected in each of the countries stratified by region with allocation of 150 for the 5 largest EU countries and 60 for the 2 Nordic countries. Random sampling continues until the target number of eligible oncology practitioners agree to participate.

With:

Stratified Random Sampling of Oncology Practitioners

In each round of survey a random sample of oncology practitioners will be selected from the sampling list in each of the countries, stratified by region, with allocation of 150 from across but not limited to the 5 largest European countries by population and 60 for 4 the Nordic countries. Random sampling continues until the target number of eligible oncology practitioners agree to participate and complete the questionnaire.

Replace:

Conduct Survey

Interviews will be conducted by telephone, internet, mail, or site visit using a standardized questionnaire with each of the eligible oncology practitioners questioned about their awareness of risk minimization measures for ONJ contained in the SPC

With:

Conduct Survey

Consenting and eligible participants will complete the study questionnaire by telephone, internet, mail, or site visit using a standardized questionnaire with each of the eligible oncology practitioners questioned about their awareness of risk minimization measures for ONJ contained in the SPC.

Section: Study Glossary

Add:

Oncology Practitioner/Specialist	**Practicing physician treating cancer patients**

Section: 3. STUDY DESIGN

Replace:

This is a multiple cross-sectional survey study of practicing oncology practitioners in the 5 largest European countries by population including France, Germany, Italy, Spain and the U.K. and 2 Nordic countries, Denmark and Sweden. The survey will be conducted for 2 rounds starting approximately 12 and 24 months after XGEVA™ becomes commercially available in each country. Before each survey round, the sampling list will be derived from lists of oncology practitioners (and their contact information). These lists are to be collected from the European Society of Medical Oncology (ESMO), from major cancer centers, oncology clinics, Cegedim (a commercial source), and other sources in each country.

With:

This is a multiple cross-sectional survey study of practicing oncology practitioners prescribing XGEVA in Europe from across but not limited to the 5 largest European countries by population (including France, Germany, Italy, Spain and the U.K). and 4 Nordic countries (including Denmark, Finland, Norway and Sweden). The survey will be conducted in two rounds. The two survey rounds will be conducted 12 to 18 months and 24 to 30 months after XGEVA becomes commercially available in the participating countries.

Replace:

Before each survey round, the sampling list will be derived from lists of oncology practitioners (and their contact information). These lists are to be collected from the European Society of Medical Oncology (ESMO), from major cancer centers, oncology clinics, Cegedim (a commercial source) and other sources in each country.

With:

Before each survey round is conducted in the participating countries, a sampling list will be derived from lists of oncology practitioners (and their contact information). These lists will be assembled by working closely with Amgen's country affiliates and Adelphi field partners to identify XGEVA prescribers.

Replace:

In each round of the survey, potential participating oncology practitioners will be selected by stratified random sampling (by country) and contacted by mail, telephone, fax, email, or site visit.

With:

In each round of the survey, potential participating oncology practitioners will be selected by stratified random sampling (by country) and contacted by mail, telephone, fax or email.

Replace:

The initial contact and screening of potential participating oncology practitioners will continue until 30 per country for a total of 210 eligible and consenting oncology practitioners are identified.

With:

The initial contact and screening of potential participating oncology practitioners will continue until a total of 210 eligible and consenting oncology practitioners are identified per survey round.

Replace:

Interviews will be conducted by telephone, internet, mail, or site visit using a standardized questionnaire with all eligible oncology practitioners to inquire about their awareness or knowledge of the risk minimization measures for ONJ contained in the SPC.

With:

The eligible oncology practitioners will complete a standardized questionnaire to collect information about their awareness or knowledge of the risk minimization measures for ONJ contained in the SPC.

Replace:

The number of oncology practitioners recruited in each country will be fixed at 30 per country per survey round stratified by region with allocation of 150 for the 5 large EU countries and 60 for the 2 Nordic countries.

With:

A sample of 150 participants from including but not limited to the 5 largest European countries by population and a sample of 60 participants from 4 Nordic countries will be sampled randomly from the country-level master list of prescrbiers per survey round.

Remove:

5 largest countries of the

Remove:

2

Replace:

Denmark and Sweden

With:

Denmark, Norway and Sweden

Add:

For the 5 largest European countries by population, it is intended that 30 oncology practitioners will be surveyed per country per survey round. If this sample size cannot be achieved, oncology practitioners from another country in that region will be surveyed to achieve a regional sample size of 150 per survey round. Oncology practitioners from the Nordic countries will be surveyed to achieve a regional sample size of 60 per survey round. For all countries, the number of surveys collected in each country in the second survey round will, where possible, equate to the number of surveys collected in each country in the first survey round.

Section: 3.1 Source Population and Selection of Participants

Replace:

The study population consists of oncology practitioners enrolled from the participating countries. To identify these oncology practitioners, contact information of oncology practitioners will be obtained from ESMO, major oncology clinics, cancer centers, Cegedim (a commercial source), and other sources in each country before the beginning of each survey round.

With:

The study population consists of oncology practitioners enrolled from the participating countries. To identify these oncology practitioners, before the beginning of each survey round contact information of oncology practitioners will be obtained from a master list of eligible respondents assembled by working with Amgen country affiliates and Adelphi field partners to identify XGEVA prescribers or centres where XGEVA is prescribed.

Replace:

In each round of the survey, the study staff will contact the sample of identified oncology practitioners through mail, telephone, fax, email, or site visit to introduce the study and to assess eligibility of each contacted person to participate in the survey.

With:

In each round of the survey, the study staff will contact the sample of identified oncology practitioners through mail, telephone, fax or email to introduce the study and to assess eligibility of each contacted person to participate in the survey. Participants who took part in the first survey round will not be included in the second round.

Replace:

These 6 attempts would consist of at least 2 different modalities of the following: at least 2 by regular mail, at least 2 by telephone call, and, potentially, other contact attempts by fax, email, or a site visit.

With:These 6 attempts would consist of at least 2 different modalities of the following: email, telephone call, and, potentially, other contact attempts by fax or email.

Replace:

The same process of sampling, contact, and screening of oncology practitioners will be conducted at approximately12 and 24 months after commercial availability of XGEVA™.

With:

The same process of sampling, contact, and screening of oncology practitioners will be conducted at approximately 12 to 18 months and 24 to 30 months after commercial availability of XGEVA.

Section: 3.2 Data Collection

Replace:

In each round of survey, interviews will be conducted by telephone, internet, mail, or site visit with each of the eligible participating oncology practitioners. The interviews will be conducted online using a standardized questionnaire following the same process in approximately 12 and 24 months after commercial availability. Interviews may be conducted up to 6 months earlier or later than these anniversaries of commercial availability in the 7 selected countries in order to consolidate the data collection for each survey round in calendar time despite the potential differences in commercial availability up to or exceeding 1 year.

With:

Each round of survey will be conducted using the standard study questionnaire (Appendix B). The survey rounds will be conducted 12 to 18 months (for survey round 1) and 24 to 30 months (for survey round 2) after commercial availability of XGEVA in each country. In each participating country, a minimum gap of 6 months will be maintained between survey rounds.

Section: 3.3 Training of Interviewers

Replace:

Each study staff member will need to complete the required training before conducting the interview.

With:

Each study staff member will need to complete the required training before conducting the study data collection.

Section: 3.4 Data Collection Instruments

Replace:

The process and materials for screening oncology practitioners for eligibility and conducting the interview with a standard questionnaire will be developed based on readability tests and expert review which may be conducted as soon as the SPC is available in the local language.

With:

The process and materials for screening oncology practitioners for eligibility and study data collection with a standard questionnaire will be developed based on readability tests and expert review which may be conducted as soon as the SPC is available in the local language.

Replace:

To ensure all questions are well targeted and correctly understood, test interviews will be conducted with the translated version of the questionnaire for each country prior to the first round of the survey by review with 2 oncology practitioners per country. The questions will be reviewed and may be modified as needed depending on the outcome of the test interviews.

With:

To ensure all questions are well targeted and correctly understood, test questionnaires will be completed with the translated version of the questionnaire for each country prior to the first round of the survey by review with 2 oncology practitioners per country. The questions will be reviewed and may be modified as needed depending on the outcome of the test questionnaires.

Section: 3.6 Potential Sources of Bias in Study Design

Add:

The number of surveys collected in each country in the second survey round will, where possible, equate to the number of surveys collected in each country in the first survey round.

Section: 4. STUDY SIZE

Replace:

A total of 210 oncology practitioners (150 from the 5 largest countries in Europe and 60 in total from Nordic countries, Denmark and Sweden) who agree to participate will be included in each cross-sectional survey and a total of 420 oncology practitioners who agree to participate will be included in the 2 cross-sectional surveys combined.

With:

A total of 210 oncology practitioners (150 from across but not limited to the 5 largest European countries by population (France, Germany, Italy, Spain and the U.K.) and 60 oncology practitioners from 4 the participating Nordic countries (Denmark, Finland, Norway and/or Sweden) who agree to participate will be included in each cross-sectional survey and a total of 420 oncology practitioners who agree to participate will be included in the 2 cross-sectional surveys combined.

Section: 5. STATISTICAL ANALYSIS

Replace:

- The above endpoints in month 12 and month 24 after commercial availability of XGEVA™ in the respective countries

With:

- The above endpoints in approximately month 12 and month 24 after commercial availability of XGEVA in the respective countries

Replace:

- Stratification of the above by the 2 regions: Nordic countries (Sweden and Denmark) versus the 5 largest European countries by population size

With:

- Stratification of the above by the 2 regions: Nordic countries (Denmark, Finland, Norway and Sweden) versus 5 largest European countries by population size

Section: 10. COMMUNICATION OF STUDY RESULTS

Replace:

Interim reports summarizing results from the survey in approximately 12 and 24 months after XGEVA™ becomes commercially available will be provided to the EMA in the next Periodic Safety Update Report (PSUR) after the analysis and summarization of results are completed.

With:

Interim reports summarizing results from the survey in approximately 18 and 30 months after XGEVA becomes commercially available will be provided to the EMA in the next Periodic Safety Update Report (PSUR) after the analysis and summarization of results are completed.

Section: Appendix B. Questionnaire for the Assessment of Physician's Knowledge of the SPC

Replace:

If response is "No", end telephone call;

With:

If response is "No", potential participant is screen failed;

Replace:

Instructions: For the following multiple choice questions, select only 1 of the choices. Only one of the 3 choices is correct regarding product recommendations.

With:

Thank you for agreeing to participate. Throughout the questionnaire, please ensure that your responses are specific and limited to your understanding of what is described in the summary of product characteristics for XGEVA® (denosumab), particularly in relation to ONJ (osteonecrosis of the jaw).

Instructions: For the following multiple choice questions, select only 1 of the choices. Only one of the 3 choices is correct regarding the summary of XGEVA® (denosumab) product recommendations. (Note: ONJ is the abbreviation used for osteonecrosis of the jaw).