STATISTICAL ANALYSIS PLAN

An Open-label, Multi-center, Phase 2 Study of Denosumab in Subjects with Giant Cell Tumor of Bone

Protocol Number 20062004

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Table of Abbreviations

Abbreviation/Acronym	Definition
BPI-SF	Brief Pain Inventory – Short Form
CR	Complete response
CSE	Clinical Summary of Efficacy
CTCAE	Common Terminology Criteria for Adverse Events (version 3)
CT	Computed tomography
DR	Disease recurrence or recurrent disease
GCTB	Giant cell tumor of bone
IP	Investigational product
MRI	Magnetic resonance imaging
PD	**Progressive disease**
PK	Pharmacokinetics
PET	Positron emission tomography
PET/CT	Positron emission tomography/ Computed tomography
PR	Partial response
SC	Subcutaneous
SD	Stable disease

1. Introduction

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol amendment 9 for denosumab study 20062004 dated **15 Dec 2017**. **This SAP version 8.0 describes the data analysis plan for conducting the final analysis. The efficacy and safety data collected through the final database lock are included in this analysis.**

2. Objectives

2.1 Primary

To evaluate the safety profile of denosumab in subjects with Giant Cell Tumor of bone (GCTB).

2.2 Secondary

- evaluation of time to disease progression in subjects with unsalvageable GCTB treated with denosumab(cohort 1)
- evaluation of the proportion of subjects who do not require surgery in denosumab treated subjects with salvageable GCTB (cohort 2)
- serum denosumab (trough) concentrations (PK subset)

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3. Study Overview

3.1 Study Design

This is a phase 2, international, multi-center, open-label study in subjects with GCTB, receiving denosumab at a dose of 120 mg SC Q4W with a loading dose of 120 mg SC on study days 8 and 15.

There are 3 cohorts in this study:

- Cohort #1: Subjects with surgically unsalvageable disease (eg, sacral, spinal GCTB, or multiple lesions including pulmonary metastases)
- Cohort #2: Subjects with surgically salvageable disease whose planned initial on-study surgery is associated with severe morbidity (eg, joint resection, limb amputation, or hemipelvectomy)
- Cohort #3: Subjects who are currently participating in Amgen study 20040215 giant cell tumor study who are eligible to enroll

3.2 Sample Size

The number of subjects in this study is governed by the number of GCTB subjects who qualify for the study. It is anticipated that approximately 530 subjects will participate, and a minimum of 20 subjects will be skeletal mature adolescents. Prior to Amendment 7, 510 subjects were enrolled. Following Amendment 7, an additional approximately 20 subjects (approximately 10 adolescents and approximately 10 adults) will be enrolled to the PK substudy.

No more than 30 subjects will enroll from the Amgen study 20040215. No adolescents will enroll into cohort 3, since all subjects participating in study 20040215 are adults (≥ 18 years of age).

Subjects will continue to receive denosumab Q4W until one of the following occurs:

- For subjects with a complete tumor resection, denosumab treatment continues for 6 doses after pathological confirmation of partial response or complete response.
- In all other cases, denosumab treatment continues until confirmation of disease progression, investigator's recommendation of discontinuation, Amgen's and Daiichi Sankyo Co., Ltd's. (for Japanese sites only) recommendation of discontinuation, the subject's decision to discontinue for any reason, or administration of any of the proscribed therapies.

In the protocol dated 15 Dec 2017, data (treatment plus follow up) will be collected for all subjects enrolled until the end of the clinical study. This is anticipated to be when subjects enrolled prior to a minimum of 60 months or until death or lost to follow-up, whichever comes first.

Subject enrollment is anticipated to occur at a rate of approximately 10 subjects per month over **the enrollment** period. This excludes subjects enrolled from the 20040215 study.

4. Study Endpoints

4.1 Primary Endpoint

The primary endpoint is the safety profile of denosumab characterized in terms of the type, frequency, and severity of adverse events and laboratory abnormalities for each cohort

4.2 Secondary Endpoints

The secondary endpoints include

- time to disease progression for cohort 1
- proportion of subjects without any surgery at month 6 for cohort 2
- **serum denosumab (trough) concentrations (PK subset)**

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5. Hypothesis

It is anticipated that denosumab, an inhibitor of RANKL, will be a well-tolerated treatment for patients with surgically unsalvageable GCTB disease, and patients with surgically salvageable disease whose planned initial on-study surgery is associated with severe morbidity.

6. Definitions

6.1 Basic Definition

Investigational Product (IP)

IP for this study refers to denosumab (excluding commercial XGEVA).

6.2 Study Points of Reference

Study Day 1

Study day 1 is the date of the administration of the first dose of IP **or the date of enrollment for subjects who are not administrated any dose of IP in 20062004 study.**

Study Day

The number of days from the study day 1 to a date of interest, inclusive:

Study day = (date of interest – study day 1) + 1.

6.3 Study Dates

Informed Consent Date

The informed consent date is the date on which a subject signs the informed consent for this study.

Enrollment Date

The enrollment date is the date on which a subject is registered as enrolled to this study.

First Dose Date

The first dose date is the date on which a subject is administered the first dose of **IP** on 20062004 study.

Last Dose Date (of a treatment phase)

The last dose date is the date on which a subject is administered the final dose of **IP (during a treatment phase).**

End of Initial Treatment Phase Date

The end of initial treatment phase date is the date recorded on the End of Study page of the Case Report Form (CRF) for an enrolled subject **(approximately 4 weeks after last dose date in the initial treatment phase).**

End of Retreatment Phase Date

The end of retreatment phase date for an enrolled subject is the date recorded on the End of Study page of the CRF in the retreatment folder for an enrolled subject (approximately 4 weeks after last dose date of retreatment phase).

End of Safety Follow-up Phase

The end of safety follow-up phase date for an enrolled subject is the date recorded on the End of Follow-up Phase page of CRF for an enrolled subject.

6.4 Study Time Intervals

Screening Period

The screening period for a subject is defined as the time from the informed consent date to the day of enrollment.

On-Study Period

The on-study period for an enrolled subject is defined as the time **from study day 1 to the end of the initial treatment phase date.**

Retreatment Phase

Subjects are considered in the retreatment phase when they **enroll in retreatment phase after initial treatment phase**.

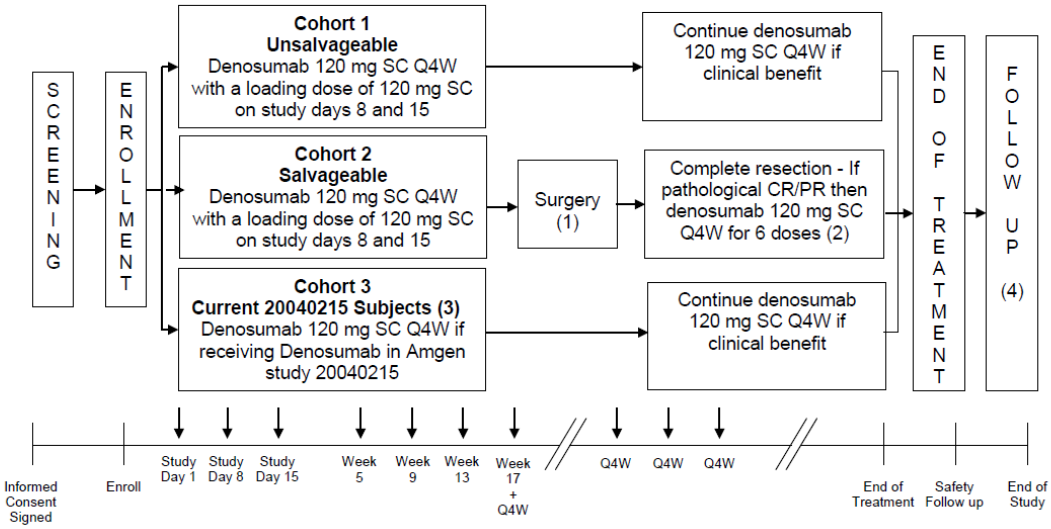
Safety Follow-up Phase (after a treatment phase)

Subjects are considered in the safety follow-up phase **after ending the initial treatment phase (or retreatment phase)** when they have an end of **initial** treatment phase date **(or end of retreatment phase date)** which is captured in the End of Study page of the CRF, and the end of study reason is not due to death, full consent withdrawn or lost to follow-up.

Treatment-Emergent Period

The treatment-emergent period for an enrolled subject is defined as the time from the first dose in the initial treatment phase to the end of the initial treatment phase (or for subjects who entered retreatment, from the first dose date in the initial treatment phase through any follow-up prior to a retreatment, until the end of retreatment phase).

Study Design and Treatment Schema



6.5 Subject Dispositions

Enrolled

Subjects are considered enrolled once all required screening assessments have been successfully completed and the eligibility criteria worksheets are signed by Amgen or Daiichi Sankyo Co., Ltd. (for Japanese sites only). **Three subjects from study 20040215 rolled over to the safety follow up phase in study 20062004**

without retreatment were excluded from all analysis sets (including the enrolled subjects set).

Exposed to Investigational Product

Subjects are defined as exposed to IP if they have received one or more doses of **IP**.

6.6 Derived Variables

Baseline Measurements

Baseline measurements are the closest recorded measurements prior to the first dose of denosumab. If there are multiple valid records on an individual at the same date and time, then the average of these records will be used. If the measurement is taken on the same day as the first dose and the exact measurement time relative to the first dose is unknown, it will be assumed to have been taken prior to the first dose of investigational product.

Change from Baseline Values

The arithmetic difference between a value of interest and a baseline value: Change from Baseline Value = (Value of Interest - Baseline Value)

Percent Change from Baseline Value

The ratio of the arithmetic difference between a value of interest and the baseline value to the baseline value multiplied by 100: Percent Change from Baseline Value = 100* [(Value of Interest - Baseline Value) / Baseline Value]

Subject Incidence Rate

The subject incidence rate for a given event is defined as the number of subjects with one or more reported occurrence of the event divided by the number of subjects who had the opportunity to experience the event.

Subject Age at Study Entry

The number of whole years from a subject's birth date to the enrollment date.

Analgesic Score

Analgesic use will be summarized using analgesic score **based on clinical's review** defined as follows.

0 = No analgesic

1 = Non-opioid analgesics

2 = Weak opioids (eg, meperidine and codeine)

3 = Strong opioids $\leq$ 75 mg oral morphine equivalent (OME) per day

4 = Strong opioids with > 75-<= 150 mg OME per day

5 = Strong opioids with > 150-<= 300 mg OME per day

6 = Strong opioids with > 300-<= 600 mg OME per day

7 = Strong opioids with > 600 mg OME per day

Analgesic score will be used as numerical value. For guidance on OME calculation and analgesic scoring derivation process and analgesic assumptions, please refer to User Manual, Opioid Analgesic Quantification for Denosumab Oncology Skeletal Related Event Clinical Studies, and Process guide for Opioid Analgesic Quantification Algorithm for Study 20090482. The User Manual will be updated before the analysis, and kept on file at Amgen.

6.7 Study Specific Definitions

Progressive Disease (PD)

It is defined as the response of progressive disease, locally recurrent disease or relapse as captured in the Disease Status page of the CRF.

Last Contact Date

The last contact date for a subject is defined as the end of initial treatment phase date, the end of retreatment phase date, the end of safety follow-up phase date, the last date on the Disease Status page of the CRF, or the last contact date or death date on the Safety Follow-Up Phase page of the CRF, whichever comes later.

Disease Progression or Recurrence during On-Study Period

It is defined as the best response of PD **during on-study period for subjects without any on-study CR/PR/SD (the response of complete response/partial response/stable disease)** or a response of PD during on-study period following an on-study CR/PR/SD.

Time to Disease Progression or Recurrence during On-Study Period

It is defined as the time interval (in days) from the first dose date to the date of **earliest** PD. If a subject has not had PD by **the end of initial treatment phase date**, time to disease progression or recurrence will be censored at her/his **end of initial treatment phase date**.

Disease Recurrence (DR) after On-Study Complete Response (CR)

It is defined as a response of PD **during the full course of clinical trial** after first on-study CR. **Subjects who do not have on-study CR will not be included in the analysis.**

Time to Disease Recurrence (DR) after On-Study Complete Response (CR)

It is defined as the time interval (in days) from the first date of CR during on-study period to the **first** date of DR **at any time during the full course of clinical trial following CR**. If a subject has not had DR following CR **by final database lock**, time to DR will be censored at her/his last contact date.

Disease Progression after Best Post-Baseline On-Study Response of Partial Response (PR)

It is defined as a response of disease progression during the full course of clinical trial after first best post-baseline on-study response of PR. Subjects who do not have on-study PR will not be included in the analysis.

Time to Disease Progression after Best Post-Baseline On-Study Response of Partial Response (PR)

It is defined as the time interval (in days) from the first date of PR during on-study period to the first date of disease progression during the full course of clinical trial following PR. If a subject has not had disease progression following PR by final database lock, time to disease progression will be censored at his/her last contact date.

Disease Progression after Best Post-Baseline On-Study Response of Stable Disease (SD)

It is defined as a response of disease progression during the full course of clinical trial after first best post-baseline on-study response of SD. Subjects who do not have on-study SD will not be included in the analysis.

Time to Disease Progression after Best Post-Baseline On-Study Response of Stable Disease (SD)

It is defined as the time interval (in days) from the first date of SD during on-study period to the first date of disease progression during the full course of clinical trial following SD. If a subject has not had disease progression following SD by final database lock, time to disease progression will be censored at his/her last contact date.

Duration of Response

It is defined as the time interval (in days) from the first date of complete response (CR) or partial response (PR) during on-study period to the first date of progressive disease (PD) at any time during the full course of clinical trial following CR or PR. If a subject has not had PD following on-study CR or PR by final database lock, time to PD will be censored at her/his last contact date. Subjects who do not have on-study CR or PR will not be included in the analysis.

Disease Progression or Recurrence after On-study GCTB Surgery

It is defined as a response of PD **during the full course of clinical trial** after first on-study GCTB surgery. **Subjects who do not have on-study surgery will not be included in the analysis. The analysis of this endpoint will be conducted by cohort.**

Time to Disease Progression or Recurrence After On-study GCTB Surgery

It is defined as the time interval (in days) from date of **first** on-study GCTB surgery to the date of first PD **during the full course of clinical trial** after on-study GCTB surgery. If a subject has not had any PD after on-study GCTB surgery **by final database lock**, time to disease progression or recurrence will be censored at her/his last contact date

Disease Progression or Recurrence after Discontinuation of IP

It is defined as a response of PD **during the full course of clinical trial** after discontinuation of **IP (ending the initial treatment phase).** Subjects **who had PD during the initial treatment phase** or who discontinued **IP** and discontinuation reason was due to consent withdrawn, lost to follow up, death, or disease progression will not be included in the analysis.

Time to Disease Progression or Recurrence after Discontinuation of IP

It is defined as the time interval (in days) from **last dose date in initial treatment phase** to the date of first PD after discontinuation of IP. If a subject has not had any PD after discontinuation of IP **by the final database lock**, time to disease progression or recurrence will be censored at her/his last contact date.

Time to On-study GCTB Surgery

It is defined as the time interval (in days) from the first dose date to the date of **first** on-study GCTB surgery. If a subject has not had any on-study GCTB surgery **by the end of initial treatment phase date**, time to on-study GCTB surgery will be censored at

her/his end of **initial treatment phase** date. **The analysis for this endpoint will be for subjects in cohort 2 only.**

Time to Second GCTB Surgery after First On-study GCTB Surgery

It is defined as the time interval (in days) from the first on-study GCTB surgery date to the date of the second GCTB surgery including surgery captured **during the full course of clinical trial**. If a subject only had one GCTB surgery by **final database lock**, time to second GCTB surgery will be censored at her/his last contact date. **Subjects who do not have any on-study surgery will not be included in the analysis**.

Progression-Free Survival Time

It is defined as the time interval (in days) from the first dose date to the date of PD or death from any cause during on-study period, whichever comes first. If a subject has not had any PD and been known to be alive by the end of initial treatment phase date, he/she will be censored at the end of initial treatment phase date.

Proportion of Subjects without Any Surgery at Month 6

It is defined as the number of subjects without any surgery **by month 6** divided by the number of cohort 2 subjects who have an opportunity to complete 6 months of treatment in the efficacy analysis set.

Proportion of Subjects Able to Undergo a Less Morbid Surgical Procedure

It is defined as the number of subjects who underwent a less morbid surgical procedure **based on clinical review of the planned versus actual surgery performed** divided by the number of subjects who had planned surgical procedures at baseline in the efficacy analysis set.

Proportion of Subjects with Pathologic Response

It is defined as the number of subjects with pathologic response divided by the number of subjects with **at least one** evaluable post-baseline pathologic sample included in the efficacy analysis set.

Proportion of Subjects without Tumor Post-baseline

It is defined as the number of subjects without tumor post-baseline divided by the number of subjects with **at least one** evaluable post-baseline pathologic sample included in the efficacy analysis set.

Radiographic Changes Over Time

It is categorized as improved, stable and worsened by the investigator's qualitative judgment. **For an individual, if multiple imaging studies are present, the best response prior to on-study GCTB surgery (for subjects undergoing surgery) or prior to the end of initial treatment phase (for subjects without on-study surgery) will be used.**

Disease Status Changes

It is categorized as complete response, partial response, stable disease and disease progression by the physician's assessment.

Time to Pain Score Change

It is defined as the time interval (in days) from the first dose date to the date of clinical meaningful pain score change (2-point decrease). If a subject has a GCTB surgery, pain score after GCTB surgery will be censored. If a subject has not had clinical meaningful pain score change by on-study GCTB surgery date **or final database lock**, time to pain score change will be censored at her/his **end of initial treatment phase date** or on-study GCTB surgery date.

7. Analysis Subsets

7.1 Safety Analysis Set

The safety analysis set, for adverse events and lab parameters, includes all enrolled subjects who received at least one dose of **IP** on 20062004 study.

7.2 Efficacy Analysis Set

The efficacy analysis set included all enrolled subjects who were eligible for the study, and received at least one dose of IP on 20062004 study. **Subjects with key inclusion/exclusion deviations of the eligibility criteria 'pathologically confirmed giant cell tumor' and/or 'known or suspected diagnosis of underlying malignancy' were excluded from the efficacy analysis set. Subjects who rolled over from Study 20040215 to the safety follow-up phase in Study 20062004 and later received retreatment were also excluded from the efficacy analysis set.**

7.3 Patient Reported Outcome (PRO) Analysis Set

Includes all subjects in the efficacy analysis set who had at least one PRO assessment and used consistent recall periods throughout the study.

7.4 PK Analysis Set

Includes all subjects who received at least one dose of **IP** with baseline PK measurement and at least one post-baseline PK measurement.

7.5 Interim Analyses Set

The Safety/Efficacy/PRO Analysis Sets are the respective analysis sets of all enrolled subjects up to the time of the interim analyses. The safety analysis set includes all enrolled subjects who received at least one dose of **IP** by the interim analysis cut-off date. The efficacy analysis set includes all enrolled subjects who were eligible for the study and received at least one dose of **IP** by the interim analysis cut-off date. The PRO analysis set includes all subjects in the efficacy analysis set who had at least one PRO assessment by the interim analysis cut-off date.

8. Interim Analysis and Early Stopping Guidelines

The first and second interim analyses were conducted after 50 and 100 subjects, respectively, had the opportunity to complete 6 months of treatment. The third interim analysis was conducted with a data cut-off date of 25 March 2011 and included approximately 286 subjects enrolled. An independent analysis of the radiographic images retrospectively collected for the study up to March 25, 2011, the data cutoff date for the CSR to be included in the GCTB filing, was performed. An external radiology vendor was selected for this retrospective radiographic image review. For analysis details and results, please see GCTB CSE SAP and the report on the integrated radiology assessments. An unplanned analysis based on agency's requested was performed based on the data cutoff date of August 30, 2013. **In addition, a planned primary analysis was conducted after subjects enrolled to the Pharmacokinetic Sub Study had an opportunity to complete 12 months of treatment (data cut-off on 24 Feb 2017).**

9. Data Screening and Acceptance

9.1 Data Handling and Electronic Transfer of Data

All data for this study will be received from Amgen's data management department. For studies in RAVE, since RAVE has no snapshot function, the study team will specify criteria to subset data for interim analysis.

9.2 Handling of Missing and Incomplete Data

Subjects may have missing data points for a variety of reasons. In general, data may be missing due to subject's early withdrawal from study, a missed visit, or non-evaluability of an endpoint at a particular point in time. For the primary outcome, no imputation will

be used. For lab results, no imputation will be used. For the PRO data outcome, primary imputation will be used.

Adverse events (AE) for which the start date is entirely missing despite Amgen's attempts to obtain the missing dates will be counted as on-treatment adverse events. Adverse events with a partially missing start date that occur prior to study day 1 will be considered pre-treatment adverse events and excluded from safety analyses. Otherwise, they will be considered as after study day 1 and included in the safety summary.

9.2.1 Missing Dates

Incomplete event start dates and concomitant medications start or stop dates will be imputed as described in the table below. If the start date is missing, assume the event or medication started before enrollment; if the stop date and the flag for medication continuing are both missing for an on-study event or medication, assume the event or medication stopped after the end of study date. Partial dates will be listed as is on the listings.

Table 1. Imputation Rules for Incomplete Dates

	Missing	Imputation	Exception
Start date (AE, concomitant medication)	Day	01	Default to study day 1 if an event starts the same year and month as study day 1
	Day / Month	01JAN	Default to study day 1 if an event started the same year as study day 1
Stop date (concomitant medication only)	Day	Last day of the month	Default to the End of Study (EOS) date or the analysis cut-off date (for ongoing subjects) if the concomitant medication stopped the same year and month as the EOS date or the analysis cut-off date for ongoing subjects respectively
	Day / Month	31DEC	Default to the EOS date or the analysis cut-off date (for ongoing subjects) if the concomitant medication stopped the same year as the EOS date or analysis cut-off date for ongoing subjects respectively

9.2.2 Missing PRO Data

The primary imputation method is:

- If there are observations before and after the missing response, take the average of the two neighboring responses to obtain the imputed value.
- If there is no observation before the missing response, apply last observation carried backward. Missing baseline will not be imputed.
- If there is no observation after the missing response, apply the worst case scenario on the subject level (eg. for 'Worst' pain, if responder criteria is ≥ 2-pt increase, then assume subject had a ≥ 2-pt increase; if responder criteria is ≥ 2-pt decrease, then assume subject did not have a ≥ 2-pt decrease).
- Baseline will not be used to impute missing post-baseline response.

9.3 Validation and Configuration Management

Programs will be developed and maintained and output will be verified according to processes described in applicable departmental and product-level procedures, including but not limited to the SOP on Configuration Management of Statistical Analysis Reporting Systems and Statistical Analysis and Reporting System Development and Validation.

Tables, listings, and graphs will be produced with standard macro programs where such macros can produce the specified outputs.

The production environment consists of Amgen-supported versions of the SAS® System and S-Plus running on the Sun Solaris operating system. The SAS version used to generate datasets and produce analyses will be documented in the clinical study report.

10. Statistical Methods of Analysis

10.1 General Principles

The statistical analysis in this open-label study will be descriptive in nature and no hypothesis testing will be performed. All the efficacy analyses will be conducted separately in each cohort and for cohorts 1 and 2 combined for all subjects in the efficacy analysis set, unless specified otherwise. **Safety analysis of adverse events will be performed by cohort and for all subjects in safety analysis set. Safety analysis of lab results will be performed by cohort and for all subjects in safety analysis set.** Some efficacy and safety analyses will be repeated for the adolescent population and adult population as applicable. PK related analysis will be conducted separately by adolescent subjects and adult subjects.

Categorical data will be presented in the form of frequency and percentage. Continuous data will be provided with the descriptive statistics, which includes n (number of

non-missing observations), mean, standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum).

10.2 Subject Accountability

For all enrolled subjects, **enrolled adolescent subjects, enrolled adult subjects and enrolled subjects in PK analysis subset,** the numbers and percentages achieving the planned assessments listed below will be tabulated by cohort:

- Subjects who received IP, who discontinued IP from initial treatment phase, and their reasons for IP discontinuation
- Subjects who enrolled in treatment phase, who discontinued the initial treatment phase, and their reason for initial treatment phase discontinuation.

For all enrolled subjects, the numbers and percentages achieving the planned assessments listed below will be tabulated by cohort:

- Subject enrollment by country and investigator
- Subjects in each key analysis set

In addition, listings will be provided for **unique manufacturing lot numbers and manufacturing lot numbers for all subjects in safety analysis sets.**

10.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first patient visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, sub-category codes and descriptions will be used during the course of the study.

Listings for important protocol deviation and all protocol inclusion/exclusion deviations will be provided for all enrolled subjects.

10.4 Demographic and Baseline Characteristics

A summary of baseline demographics for all enrolled subjects, **enrolled adolescent subjects, enrolled adult subjects and enrolled subjects in PK analysis subset** will include: age, sex, race, and geriatric age group (if applicable).

A summary of baseline physical characteristics for all enrolled subjects, **enrolled adolescent subjects, enrolled adult subjects** will include: weight, height, and body mass index.

A summary of baseline laboratory parameters for all enrolled subjects will include: Albumin-adjusted calcium, albumin, magnesium, phosphorus, and creatinine.

A summary of baseline disease characteristics for all enrolled subjects, **enrolled adolescent subjects, enrolled adult subjects and enrolled subjects in PK analysis subset** will include: Karnofsky performance status score, GCTB disease type (primary resectable, primary unresectable, recurrent resectable, or recurrent unresectable), the longest dimension and location of the target lesion, and planned surgery.

A summary of prior treatments for all enrolled subjects will include the use of following for the initial GCTB**,** bisphosphonate therapy, radiation therapy, chemotherapy, and surgeries for GCTB.

A summary of prior GCTB history for all enrolled subjects will include time from initial GCTB to enrollment, initial GCTB lesion location and prior GCTB surgery location.

A summary of baseline BPI-SF outcome scores for all enrolled subjects will include: ‘‘pain at its worst’ score, pain severity score, and pain interference score.

Baseline analgesic use will also be summarized.

All analyses mentioned in this section will be conducted by cohort and for all subjects unless otherwise specified. The analyses for PK subset will be provided by adolescent and adult subjects and for all subjects in the PK analysis set.

10.5 Efficacy Analyses

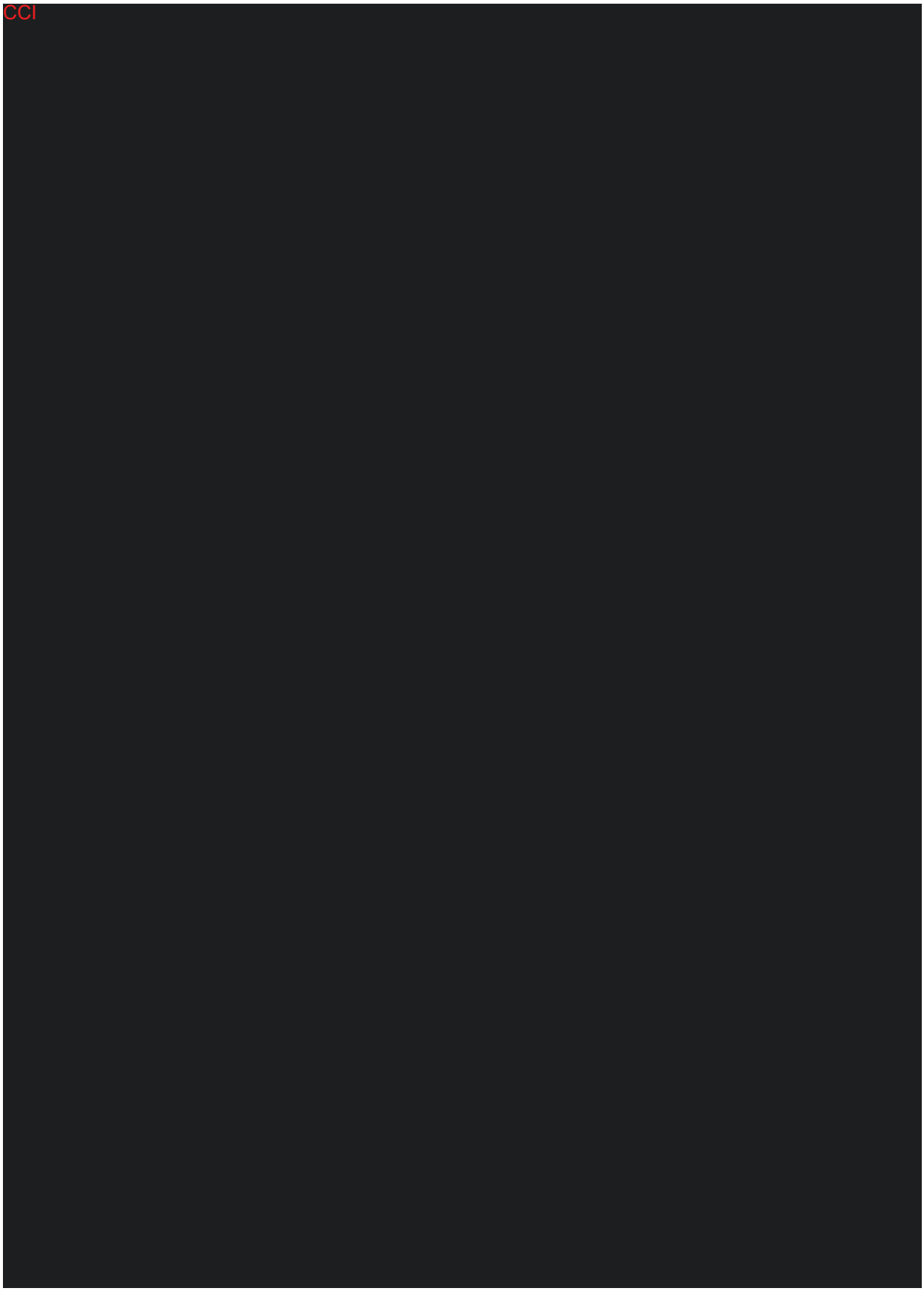
10.5.1 Analyses of Key Efficacy Endpoints

Time to Disease Progression for Cohort 1

Kaplan-Meier estimates will be graphically displayed. Kaplan-Meier event rates at various time points (eg, month 6, month 12, etc) with 2-sided confidence intervals will be summarized. In addition, Kaplan-Meier estimates of quartiles (median, 25th and 75^{th} percentiles) with 2-sided 95% confidence intervals will be calculated if applicable. This analysis will be conducted for adolescent subjects, adult subjects and all subjects in the efficacy analysis set.

Proportion of Subjects Without Any Surgery at Month 6 for Cohort 2

Crude estimates with 2-sided exact 95% confidence intervals will be summarized for cohort 2 subjects who have an opportunity to complete 6 months of treatment in the efficacy analysis set. This analysis will be conducted for adolescent subjects, adult subjects and all subjects from cohort 2 in the efficacy analysis set.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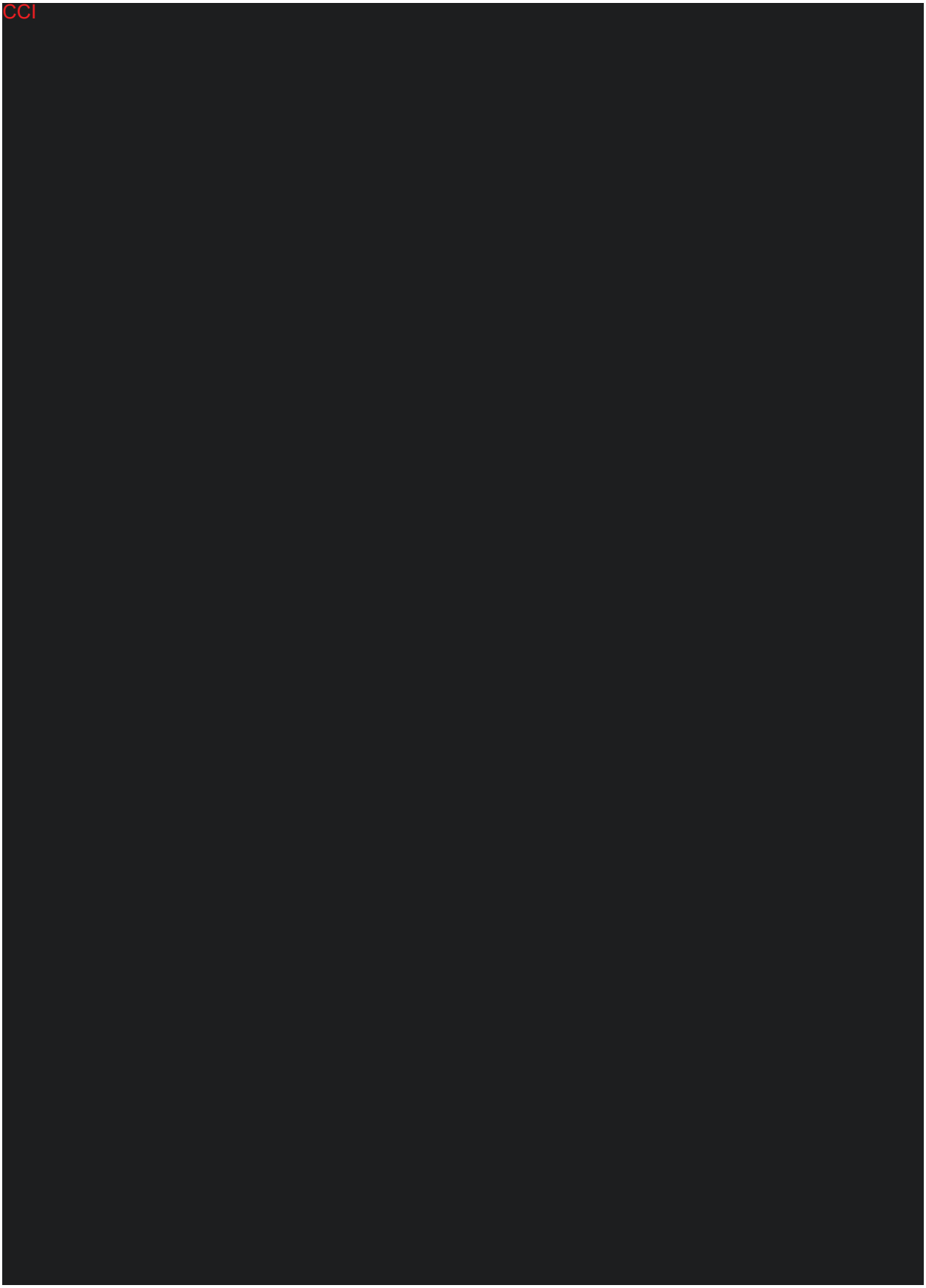

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10.6 Safety Analyses

10.6.1 Adverse Events

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 10.0 or higher.

Treatment-emergent adverse events include all adverse events that occurred from the first dose in the initial treatment phase to the end of the initial treatment phase (or for subjects who entered retreatment, from the first dose date in the initial treatment phase through any follow-up prior to a retreatment, until the end of retreatment phase). Adverse events that occurred after the treatment-emergent period are summarized separately (Section 10.6.3).

The summary of treatment-emergent adverse events will be provided for the following categories by system organ class, **high level term** and preferred term in descending order of frequency, and by preferred term in descending order of frequency.

- All treatment-emergent adverse events
- IP related treatment-emergent adverse events
- CTCAE grade 3, 4, or 5 treatment-emergent adverse events
- IP related CTCAE grade 3, 4, or 5 treatment-emergent adverse events
- Treatment-emergent serious adverse events
- IP related treatment-emergent serious adverse events
- Treatment-emergent adverse events leading to treatment phase discontinuation
- IP related treatment-emergent adverse events leading to treatment phase discontinuation
- Treatment-emergent adverse events leading to IP discontinuation
- Treatment-emergent fatal events

The analysis will be provided by cohort and for all subjects in the safety analysis set.

10.6.2 Adverse Events of Interest

Protocol-specified adverse events of interest namely, positively adjudicated atypical femoral fracture (AFF), positively adjudicated osteonecrosis of the jaw (ONJ) and new malignancy events were evaluated during and after the treatment-emergent period of the study.

Other adverse events of interest namely musculoskeletal pain, osteonecrosis outside the jaw, hypocalcaemia, adverse events potentially associated with hypersensitivity, infection, cardiac disorders and vascular disorders were evaluated during the treatment-emergent period of the study. Hypercalcaemia events that occurred after 30 days following the last dose of IP in the initial treatment phase were also evaluated as an event of interest.

Malignancy type (ie, new malignancies, and new malignancy in GCTB) will be determined by medical review.

The incidences of all adverse events of interest by cohort and for all subjects in safety analysis set will be summarized, and discussed in the clinical study report.

Subject-year adjusted rate of adjudicated positive ONJ will be summarized by cohort and for all subjects in the safety analysis set by time period.

10.6.3 Adverse Events Occurred After Treatment-emergent Period

Subject incidence of adverse events and adverse events related to investigational product which occurred after the treatment-emergent period will be provided for all adverse events, serious adverse events, fatal adverse events, grade ≥ 3 (ie, CTCAE grade 3, 4, or 5) adverse events, adverse events leading to treatment phase discontinuation, and adverse events leading to investigational product discontinuation.

The summary of all adverse events and serious adverse events after the treatment-emergent period will be provided by system organ class, high level term and preferred term in descending order of frequency, and by preferred term in descending order of frequency.

The summary of adverse events leading to treatment phase discontinuation and fatal adverse events after the treatment-emergent period will be provided by preferred term in descending order of frequency.

All analyses in this section will be conducted by cohort and for all subjects in the safety analysis set and at risk for this analysis.

Subjects who rolled over to study 20062004 safety follow-up phase and does not receive IP on 20062004 study are excluded from safety analysis set. Their safety data will be reported in a separate listing.

10.6.4 Adverse Events for Adolescent Subjects

Subject incidence of treatment-emergent adverse events and treatment-emergent adverse events related to investigational product will be provided for all adverse events, serious adverse events, fatal adverse events, grade ≥ 3 (ie, CTCAE grade 3, 4, or 5) adverse events, adverse events leading to treatment phase discontinuation, and adverse events leading to investigational product discontinuation.

The summary of all treatment-emergent adverse events and treatment-emergent serious adverse events will be provided by system organ class, high level term and preferred term in descending order of frequency, and by preferred term in descending order of frequency.

Subject incidence of adverse events and adverse events related to investigational product which occurred after the treatment-emergent period will be provided for all adverse events, serious adverse events, fatal adverse events, grade ≥ 3 (ie, CTCAE grade 3, 4, or 5) adverse events, adverse events leading to treatment phase discontinuation, and adverse events leading to investigational product discontinuation.

The summary of all adverse events after treatment-emergent period and serious adverse events after treatment-emergent period will be provided by system organ class, high level term and preferred term in descending order of frequency, and by preferred term in descending order of frequency.

Subject incidence of adverse events of interest and new malignancy in GCTB will be tabulated.

All analyses in this section will be conducted by cohort and for all adolescent subjects in the safety analysis set.

10.6.5 Adverse Events for Adult Subjects

Subject incidence of treatment-emergent adverse events and treatment-emergent adverse events related to investigational product will be provided for all adverse events, serious adverse events, fatal adverse events, grade ≥ 3 (ie, CTCAE grade 3, 4, or 5) adverse events, adverse events leading to treatment phase discontinuation, and adverse events leading to investigational product discontinuation.

Subject incidence of adverse events and adverse events related to investigational product which occurred after the treatment-emergent period will be provided for all adverse events, serious adverse events, fatal adverse events, grade ≥ 3 (ie, CTCAE grade 3, 4, or 5) adverse events, adverse events leading to treatment phase discontinuation, and adverse events leading to investigational product discontinuation.

Subject incidence of adverse events of interest and new malignancy in GCTB will be tabulated.

All analyses in this section will be conducted by cohort and for all adult subjects in the safety analysis set.

10.6.6 Laboratory Test Results

Laboratory parameters will be summarized over time using descriptive statistics for recorded values and change from baseline. In addition, CTCAE grade shift tables, in which the incidence of shift of toxicity grades in recorded values from baseline to “worst” on-study value is displayed, will also be provided. All analyses in this section will be conducted by cohort and for all subjects in the safety analysis set

10.6.7 Immunogenic Response

Immunogenic response will be described by tabulating the numbers of subjects who tested positive (binding, neutralizing) for anti-denosumab antibodies in the subjects

receiving at least one dose of IP and had at least one antibody sample. Subjects who test positive for either binding or neutralizing antibodies against denosumab will be interpreted as persistently positive if the antibody status remains positive on repeat testing. If a subject tests positive for neutralizing antibodies against denosumab, the relationship between the presence of neutralizing antibodies and adverse events will be evaluated.

10.6.8 Exposure to Investigational Product

The number and percentage of subjects receiving various numbers of doses will be summarized for all enrolled subjects, enrolled adolescent subjects and enrolled subjects in PK analysis subset who received ≥ 1 dose of investigational product for initial treatment phase and **full course of clinical trial separately.**

10.6.9 Concomitant Medications and Safety Follow Up Intervention

Subject incidence of concomitant medications will be summarized by preferred term for all subjects in the safety analysis set.

Subject incidence of safety follow-up interventions and retreatment will be summarized by cohort and for all subjects in the safety analysis set who ever entered safety follow up

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12. Literature Citations / References

Fairclough D.L, Gagnon D, and Papadopoulos G. Planning Analyses of Quality-of-Life Studies: A Case Example with Migraine Prophylaxis. J. Biopharm Stat 2004;14:31–51

13. Appendices

Appendix A. Reference Values / Toxicity Grades

The Common Terminology Criteria for Adverse Events (CTCAE) are available at the following link:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf.

Appendix B. BPI-SF

Question Mapping

MEASURES (scale)	QUESTIONS
Pain Interference	8a-8g
Pain Severity	3-6

Scoring Algorithm

The scoring algorithm of the BPI-SF questionnaire generates two measures based upon the subdomains of pain severity and pain interference. Measures of severity are scored by reports of experiencing the "worst pain" or computing the arithmetic mean of the 4 severity items. Measures of interference are scored by the arithmetic mean of the 7 interference items.

When calculating subscale scores by taking the arithmetic mean, ie, the pain severity and pain interference scores, make sure that the majority of the items are responded to. For example, 3 out of 4 pain severity and 4 out of the 7 pain interference would represent the majority of the items for the subscale. If there are less than the indicated items, we consider the subscale 'missing'.