# A PHASE 3 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY OF THE ANALGESIC EFFICACY AND SAFETY OF THE SUBCUTANEOUS ADMINISTRATION OF TANEZUMAB (PF-04383119) IN SUBJECTS WITH CANCER PAIN PREDOMINANTLY DUE TO BONE METASTASIS RECEIVING BACKGROUND OPIOID THERAPY

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| **Compound:** | PF-04383119 |
| **Compound Name:** | Tanezumab |
| **United States (US) Investigational New Drug (IND) Number:** | CCI [redacted] |
| **European Clinical Trials Database (EudraCT) Number:** | 2013-002223-42 |
| **Protocol Number:** | A4091061 |
| **Phase:** | 3 |

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## Document History

| Document | Version Date | Summary of Changes |
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| Amendment 4 | 14 June 2018 | Rationale for Protocol Amendment 4. Added background and rationale for key changes in Amendment 4.<br><br>Study Design and Study Treatments. Updated to reflect enrolment and revised statistical methods.<br><br>Statistical Methods. Interim analysis and final sample size revised.<br><br>Section 3. Study Design. Figure 1. Revised to reflect change in sample size. Updated to reflect change to interim analysis and sample size.<br><br>Section 4.2. Exclusion Criteria. Criterion 5. Prohibited medications revised.<br><br>Section 4.2. Exclusion Criteria. Criterion 16c. Updated for clarification.<br><br>Section 4.4. Lifestyle Guidelines. Clarification of contraception method 5. Sexual abstinence added.<br><br>Section 5.5. Administration. Clarification of medication error added.<br><br>Section 5.6. Investigational Product Storage. Clarification of medication error added.<br><br>Section 5.8.1.1. Prohibited Background Opioid Treatment. Clarification added regarding prohibited opioids.<br><br>Section 5.8.1.3. Restrictions on Use of Treatments for Underlying Cancer or Bone Metastasis. Clarification regarding prohibited medication added.<br><br>Section 5.8.2.3. Permitted Concomitant Treatments for Underlying Cancer or Bone Metastasis. Updated to reflect revised |

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| | | prohibited medications.<br><br>Section 9.1. Sample Size Determination. Interim analysis and sample size revised.<br><br>Section 9.2.1. Primary Endpoint Analysis. Clarification added.<br><br>Section 9.6. Interim Analysis. Interim analysis and sample size revised.<br><br>Section 9.7.1.1. Serious Adverse Events. Pre-specified serious adverse events revised.<br><br>Section 9.7.1.2. Events consistent with Hy's Law. Hy's Law section added.<br><br>Appendix 1. List of Abbreviations. Updated to reflect terms added.<br><br>CCI [redacted]<br><br>Appendix 8. Restrictions on Prior and Concomitant Medications. Opioids. Clarification added regarding prohibited opioids.<br><br>Appendix 8. Restrictions on Prior and Concomitant Medications. Chemotherapeutic, Radiopharmaceutical or Radiotherapy, Anti-Cancer Hormonal Treatments. Updated to reflect revised prohibited medications.<br><br>Appendix 8. Restrictions on Prior and Concomitant Medications. Biologics. Clarification added regarding prohibited medications. |
| Amendment 3 | 02 February 2017 | Rationale for Protocol Amendment 3. Added to provide background and rationale for key changes in Amendment 3.<br><br>Protocol Summary. Background and Rationale. Updated to include background on prior studies. |

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| | | Objectives and Endpoints. Primary objective revised to remove tanezumab 10 mg dose comparison. Secondary objective revised to remove tanezumab 10 mg dose comparison.<br><br>Study Design and Study Treatments. Updated to reflect removal of tanezumab 10 mg dose arm.<br><br>Statistical Methods. Updated to reflect removal of tanezumab 10 mg dose arm.<br><br>Table 1. Pre-Treatment, Double-Blind & Safety Follow-Up Schedule of Activities & Table 2. Early Termination Schedule of Activities. Footnotes updated to reflect changes to protocol activities.<br><br>Section 1.2.5. Dose Selection Rationale. Updated to reflect removal of tanezumab 10 mg dose arm and include information on prior studies.<br><br>Section 1.2.8. Rationale for Population. Updated to include rationale for expanding primary tumor types.<br><br>Section 1.2.9. Benefit vs Risk for the Study Population. Updated to reflect removal of tanezumab 10 mg dose arm and expanding tumor types.<br><br>Section 2.1.1. Primary Objective. Updated to reflect removal of tanezumab 10 mg dose arm.<br><br>Section 2.1.2. Secondary Objective. Updated to reflect removal of tanezumab 10 mg dose arm.<br><br>Figure 1. Study Design. Figure updated to reflect revised study design without tanezumab 10 mg dose arm.<br><br>Section 3. Study Design. Updated to reflect removal of tanezumab 10 mg dose arm.<br><br>Section 4.1. Inclusion Criteria, Item 4. Body |

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| | | weight revised.<br><br>Section 4.1. Inclusion Criteria, Item 5. Primary cancer types expanded.<br><br>Section 4.1. Inclusion Criteria, Item 6. Imaging modality requirement for bone scan confirmation of bone metastasis revised.<br><br>Section 4.1. Inclusion Criteria, Item 13. Criterion for adequate renal function revised and clarified.<br><br>Section 4.2. Exclusion Criteria, Item 3. Clarification of test process.<br><br>Section 4.2. Exclusion Criteria, Item 5; Section 5.8.; Section 6.2.2.2. Dose stability window requirement for concomitant treatments for underlying cancer or bone metastasis revised. Restrictions on use clarified.<br><br>Section 4.2. Exclusion Criteria, Item 6. Exclusionary window requirement for receipt of radiopharmaceutical treatment or radiotherapy for treatment of bone metastasis revised.<br><br>Section 4.2. Exclusion Criteria, Item 7. Dose stability window requirement for concurrent adjuvant analgesics revised.<br><br>Section 4.2. Exclusion Criteria, Item 9. Clarification regarding diagnostic criteria for shoulder osteoarthritis added.<br><br>Section 4.2. Exclusion Criteria, Item 12. Clarification regarding permitted radiographic findings added.<br><br>Section 4.2. Exclusion Criteria, Item 16. Clarification regarding diagnosis of paraneoplastic syndrome added.<br><br>Section 4.2. Exclusion Criteria, Item 28. Exlusionary time period for participation in other studies updated. |

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| | | Section 5.1. Allocation to Treatment. Updated to reflect removal of tanezumab 10 mg dose arm.<br><br>Sections 5.3, 6.2.2.1, and 7.1.2. Clarification regarding capture of background opioid use added.<br><br>Section 5.4.1.2. Placebo for Tanezumab and Section 5.4.2. Preparation and Dispensing. Updated to reflect removal of tanezumab 10 mg dose arm.<br><br>Section 5.6. Investigational Product Storage. Temperature monitoring of Investigational Product Storage updated.<br><br>Sections 5.8.1 and 6.2.2.2. Use of prohibited concomitant treatments including opioid, non-opioid, other and underlying cancer or bone metastasis therapies revised.<br><br>Section 5.8.2. Use of permitted concomitant treatments including non-opioid, anticancer therapies revised. Clarification regarding use and reimbursement of standard of care analgesia added.<br><br>Section 6.1. Re-screening process revised. Clarification regarding inclusion/exclusion criteria assessment, and Screening activities added.<br><br>Section 6.1.1.1.1. Assessment of Inclusion and Exclusion Criteria. Updated to reflect permitted bone metastasis imaging.<br><br>Section 6.1.1.2.2. Schedule Screening X rays of Major Joints. Clarification added regarding Screening x-ray assessments.<br><br>Section 6.1.1.2.4. Adjustment of Background Opioid Regimen. Clarification added regarding Screening activities.<br><br>Section 6.2.2.2. Concomitant Treatment for Underlying Cancer or Bone Metastasis. Clarification added regarding permitted |

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| | | concomitant treatments.<br><br>Section 6.3. Safety Follow-Up Period. Updated to reflect changes to permitted concomitant treatments.<br><br>Section 6.4. Subject Withdrawal/Early Termination. Clarification added regarding permitted concomitant treatments.<br><br>Section 7.1.1.2. Non-index Site(s) of Cancer Pain Assessment. Typographical error corrected.<br><br>Section 7.1.2. Subject Daily/Weekly Opioid Medication Use. Clarification added regarding recording opioid use.<br><br>Section 7.2.4. Eastern Cooperative Oncology Group (ECOG) Performance Status. Completion of assessment updated.<br><br>Section 7.4.4. Evaluation and Follow-Up for Increased, Severe Persistent Joint Pain. Clarification added regarding evaluation and follow-up for subjects who report new or worsened joint pain.<br><br>Section 9.1. Sample Size Determination. Updated to reflect removal of tanezumab 10 mg dose arm.<br><br>Section 9.2. Efficacy Analysis. Updated to reflect removal of tanezumab 10 mg dose arm.<br><br>Section 9.2.1. Primary Endpoint Analysis. Updated to reflect removal of tanezumab 10 mg dose arm. Definition of secondary efficacy population (Per Protocol) updated.<br><br>Section 9.3.4. Opioid Use and Opioid Adverse Effects Analysis. Updated to reflect plan for data analysis of discontinued tanezumab 10 mg dose arm.<br><br>Section 9.4. Safety Analysis. Updated to reflect plan for data analysis of discontinued |

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| | | tanezumab 10 mg dose arm.<br><br>Section 16. References. Updated to reflect additional references.<br><br>Section 101. Substudy Introduction. Clarification added regarding protocol-required procedures.<br><br>Section 104.2. Life Style Guidelines. Clarification regarding contraception requirements in the substudy added.<br><br>Section 106.1. Baseline Visit (Last Visit in Study A4091061 or when Notified of TJR Surgery). Clarification added regarding assessments.<br><br>Tables 1 & 2. Main table and footnote text revised in line with changes to protocol.<br><br>Appendix 1. List of Abbreviations. Updated to reflect additional imaging modality.<br><br>Appendix 4. American College of Rheumatology (ACR) Classification Criteria for Osteoarthritis. Clarification added regarding ESR testing.<br><br>CCI [redacted]<br><br>Appendices 7 and 8. Guidance regarding analgesics and concomitant medications updated in line with changes to protocol.<br><br>Administrative clarifications and typographical corrections have been incorporated throughout. |
| Amendment 2 | 02 November 2015 | Sections 4.2 and 5.8.2.3. In Japan only, chemotherapies associated with peripheral neuropathy are prohibited from Screening to Week 32.<br><br>Sections 3, 6.3 and 6.3.2, and Schedule of Activities, Table 1. Week 40 will be a clinic |

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| | | visit for subjects in Japan.<br><br>Sections 6, 6.2.2.4 and 7.3.9, and Schedule of Activities, Table 1. At Week 16, subjects in Japan will have X-rays of joints; typo correction.<br><br>Section 7.3.9.1. Radiation exposure has been added for subjects in Japan.<br><br>Appendix 18. For France Contrat Unique has been added. |
| Amendment 1 | 18 August 2015 | Section 4.1. Inclusion Criteria, item 16. Update to contraceptive requirements.<br><br>Section 4.2. Exclusion Criteria, item 29. Update to contraceptive requirements.<br><br>Section 4.4. Lifestyle Guidelines. Update to acceptable methods of contraception.<br><br>Section 16. References. Addition of citation for contraception methods.<br><br>Section 104.2. Life Style Guidelines. Update to contraceptive requirements.<br><br>Appendix 1. List of Abbreviations. Addition of intrauterine system (IUS). |
| Original protocol | 10 April 2015 | Not Applicable (N/A) |

This amendment incorporates all revisions to date, including amendments made at the request of regulatory authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

## RATIONALE FOR PROTOCOL AMENDMENT 3

### Background

The original A4091061 protocol was issued with a version date of 10 April 2015. The protocol was subsequently amended as follows:

- Amendment 1, 18 August 2015: in response to comments received during assessment of the initial clinical trial application (CTA) for A4091061 via the European Union (EU) Voluntary Harmonisation Procedure (VHP684 [VHP2015072]), the protocol was amended with respect to contraceptive requirements.

- Amendment 2, 2 November 2015: the schedule of activities for subjects in Japan was modified following comments received from the Pharmaceuticals and Medical Devices Agency (PMDA).

### Study Status

As of 1 January 2017, a total of 54 investigational sites have been opened in the following countries: Australia, Austria, Czech Republic, Hungary, Japan, Poland, Romania, Slovakia, South Korea, Spain and United Kingdom (UK).

The A4091061 protocol achieved first subject first visit (FSFV) in October 2015. As of 1 January 2017, only 17 of the required 255 subjects have been randomized, and, moreover, no subjects were randomized during October or November 2016.

In summary, there have been extensive recruitment challenges with this study to date, despite the Sponsor's efforts to train investigators and motivate sites. In order to address these challenges, the protocol has been amended (Amendment 3) in order to optimize clinical and operational feasibility, with details provided below.

### Amendment 3

The most common reason cited by study investigators for the slow enrollment, thereby making the study so difficult to conduct, was that several of the entry criteria were unnecessarily restrictive. Therefore, Amendment 3 includes modifications to the entry criteria in order to more accurately reflect the real-world population and the clinical management of patients with metastatic bone pain. These modifications are intended to make the study operationally feasible while still maintaining benefit-risk for the recruited subjects.

Key changes include:

- Removal of the restriction on permitted primary tumor types to allow any primary tumor type so long as there is a documented bone metastasis.

- Less restrictive body weight and renal function inclusion criteria.

- Expansion of acceptable imaging modalities for demonstration of a bone metastasis.

- Broader permitted concomitant medications for cancer therapies, and less restrictive timeframe for use both prior to randomisation and also during weeks 8-24 of the double blind treatment period (i.e. after the primary endpoint data have been collected).

**Removal of 10 mg dose treatment arm**

During the process of amending the protocol, the utility of including the 10 mg dose arm was reassessed.

In the previous cancer pain study (A4091003), tanezumab at 10 mg did not demonstrate a significant improvement versus placebo on the primary efficacy endpoint of the change from Baseline to Week 6 in the daily average pain intensity. However, there was evidence of efficacy for tanezumab 10 mg in post-hoc subgroup analyses of subjects with Baseline pain scores >5 and Baseline opioid use below the median value for the study (60 mg/day in morphine equivalents). Also, in subjects with Baseline pain scores >5 irrespective of Baseline opioid use, a meaningful treatment difference was demonstrated, indicating that it may be possible to demonstrate tanezumab efficacy in subjects with painful bone metastasis under different study conditions.

Considering the preliminary evidence for tanezumab 10 mg efficacy in cancer pain subjects, it was hypothesized that study A4091061 would provide confirmatory evidence of efficacy for the 10 mg dose in the current study. However, since the original A4091061 protocol was written, a study with another nerve growth factor (NGF) inhibitor, fulranumab, has been published which also failed to demonstrate a treatment benefit in the primary endpoint of pain intensity in cancer pain[1].

Although the fulranumab data have not yet appeared in a peer-reviewed journal, given the totality of the available clinical data on NGF inhibition in cancer pain, the observation that higher doses of tanezumab are needed in certain pain models to provide clinically significant efficacy (e.g. painful diabetic neuropathy vs. chronic lower back pain vs. osteoarthritis), good tolerability in previous cancer pain trials and the very slow enrollment rate with the current study design, further investigation of tanezumab at the lower dose of 10 mg will not be conducted. Therefore, the revised study will only investigate the higher dose of 20 mg for which the Sponsor considers there is a reasonable probability of achieving clinically relevant efficacy in cancer pain without additional risk. Subjects who have been randomized to the 10 mg dose treatment arm, and who are in the double-blind treatment period at the time of implementation of Amendment 3, will be administered 20 mg for any remaining doses.

**Summary**

The changes incorporated into Amendment 3, which have been based upon feedback from investigators, optimize benefit-risk for the subjects and more accurately reflect standard of care clinical practice in the real world. The changes maintain high standards of scientific integrity and are essential in order to enable study execution. Cancer pain is an area of significant unmet medical need, and therefore Amendment 3 is proposed to overcome study

obstacles, as described, and to facilitate potential delivery to patients of a new drug, should the study yield positive results.

## RATIONALE FOR PROTOCOL AMENDMENT 4

The changes incorporated into Amendment 4 reflect feedback provided by the United States (US) Food and Drug Administration (FDA) in May 2018.

Interim Analysis and final sample size modifications have been made in order to facilitate futility or efficacy decision-making.

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## PROTOCOL SUMMARY

## BACKGROUND AND RATIONALE

Tanezumab is a monoclonal antibody that binds to and inhibits the actions of nerve growth factor (NGF). The Nerve Growth Factor Inhibitor (NGFI) class may offer an important breakthrough in the treatment of chronic pain and is under clinical investigation for the treatment of pain associated with osteoarthritis or other chronic pain conditions. Information regarding development of tanezumab in non-cancer patient populations can be found in the tanezumab investigator brochure[2] and in publically-available documents prepared for the United States (US) Food and Drug Administration (FDA) Arthritis Advisory Committee meeting on March 12, 2012.[3 4,5.]

The rationale for treatment of tanezumab in subjects with metastatic bone pain is provided by the rich innervation of bone by NGF-responsive neurons,[33] the pathologic elevation of NGF and NGF-responsive neurons in bone metastases,[33] results of preclinical studies demonstrating metastatic bone pain efficacy with the murine precursor antibody to tanezumab (MAb 911) and results of tanezumab clinical studies in musculoskeletal and visceral pain conditions.[2]

The efficacy of tanezumab in subjects with painful bone metastasis has been evaluated in Study A4091003, which was a randomized, double-blind, placebo-controlled, parallel group study in subjects with cancer pain due to bone metastasis who were receiving background treatment with opioids.[43] In addition, subjects who had been randomized and treated in Study A4091003, and who wished to receive open-label tanezumab therapy, could roll over to Study A4091029, a safety extension study designed to investigate the safety and maintenance of effect of tanezumab 10 mg.[44] In Study A4091003, a total of 59 patients were treated with either a single intravenous (IV) dose of tanezumab 10 mg (N=29) or placebo (N=30). In Study A4091029, a total of 41 patients were treated with tanezumab 10 mg IV.

A positive outcome for the primary efficacy endpoint for Study A4091003 (ie, a statistically significant change from Baseline to Week 6 in the daily average pain intensity) was not achieved, although the mean decrease from Baseline in the tanezumab 10 mg IV treatment group was numerically greater than that for the placebo treatment group. The change from Study A4091003 Baseline in average pain was maintained up to Week 24 in A4091029 for all subjects. For the 6 subjects who had received placebo in Study A4091003, the average pain score in A4091029 subsequently worsened from Week 24 to Week 40 (back to the Study A4091003 Baseline pain level). However for subjects who had received tanezumab 10 mg in Study A4091003, the improvement in average pain was further maintained to Week 40 of Study A4091029.

Although an acceptable safety profile was seen in the previous studies in this patient population, efficacy has not yet been robustly demonstrated, hence further evaluation of benefit-risk is required in Study A4091061.

## OBJECTIVES AND ENDPOINTS

### Primary and Secondary Objectives

The primary objective of Study A4091061 is to demonstrate superior analgesic efficacy of tanezumab 20 mg subcutaneous (SC) versus matching placebo SC at Week 8 in subjects with cancer pain predominantly due to bone metastasis receiving background opioid therapy.

The secondary objective is to evaluate the safety of tanezumab 20 mg SC versus matching placebo SC in subjects with cancer pain predominantly due to bone metastasis receiving background opioid therapy.

### Primary and Secondary Endpoints

The primary efficacy endpoint is the change from Baseline to Week 8 in the daily average pain intensity Numeric Rating Scale (NRS) score in the index bone metastasis cancer pain site.

The secondary endpoints are as follows:

Efficacy Measures

- Change from Baseline to Weeks 1, 2, 4, 6, 12, 16 and 24 in the daily average pain intensity NRS score in the index bone metastasis cancer pain site.
- Change from Baseline to Weeks 1, 2, 4, 6, 8, 12, 16 and 24 in the daily worst pain intensity NRS score in the index bone metastasis cancer pain site.
- Change from Baseline to Weeks 1, 2, 4, 6, 8, 12, 16 and 24 in the weekly average pain intensity NRS score in non-index cancer pain sites.
- Change from Baseline to Weeks 1, 2, 4, 6, 8, 12, 16 and 24 in the weekly worst pain intensity NRS score in non-index cancer pain sites.
- Change from Baseline to Weeks 1, 2, 4, 6, 8, 12, 16 and 24 in the daily average pain intensity NRS score in the non-index visceral cancer pain sites.
- Change from Baseline to Weeks 1, 2, 4, 6, 8, 12, 16 and 24 in the daily worst pain intensity NRS score in the non-index visceral cancer pain sites.
- [redacted]
- [redacted]

- Response as defined by a ≥30%**,** ≥50%, ≥70%, and ≥90%, reduction from Baseline in the daily average and daily worst pain intensity NRS score in the index bone metastasis cancer pain site at Weeks 1, 2, 4, 6, 8, 12, 16 and 24.

- Change from Baseline in Patient's Global Assessment of Cancer Pain at Weeks 2, 4, 8, 16 and 24.

- Response as defined by an improvement of ≥2 points in Patient's Global Assessment of Cancer Pain at Weeks 2, 4, 8, 16 and 24.

- [redacted]

- [redacted]

Opioid Use and Opioid Adverse Effects Measures

- Average daily total opioid consumption (in mg of morphine equivalent doses) at Weeks 1, 2, 4, 6, 8, 12, 16 and 24.

- Average number of doses of rescue medication required per week at Weeks 1, 2, 4, 6, 8, 12, 16 and 24.

- Change from Baseline in the weekly Opioid-Related Symptom Distress Scale at Weeks 2, 4, 8, 16 and 24.

Safety Measures

- Adverse events.

- Standard safety assessments (safety laboratory testing [chemistry, hematology], sitting vital signs, electrocardiogram [ECG, 12-lead]).

- Orthostatic (supine/standing) blood pressure assessments.

- Weight measurements.

- Physical examinations.

- Joint safety adjudication outcomes.

- Total joint replacements.

- [redacted]

- [redacted]

- Anti-drug antibody (ADA) assessments.

CCI [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

## STUDY DESIGN AND STUDY TREATMENTS

The study is designed with a post-randomization study duration of 48 weeks and will consist of three periods: Pre-Treatment, Double-Blind Treatment and 6-month Safety Follow-Up. The Pre-Treatment Period lasting 5-37 days will be used to determine subject eligibility, followed by a Double-Blind Treatment Period lasting 24 weeks (Days 1-169) and a 6-month Safety Follow-Up Period ending with the End of Study Visit at Week 48 (Day 337).

The protocol was initially designed to include 3 treatment groups (tanezumab 20 mg SC, tanezumab 10 mg SC, and placebo), and was amended (Amendment 3) after study start to discontinue the tanezumab 10 mg dose arm. It is estimated that approximately 11 subjects in total were randomized to receive tanezumab 10 mg SC prior to implementation of Amendment 3.

Following implementation of Amendment 3, subjects were randomized in a 1:1 ratio (planned 85 subjects/arm) to one of two treatment arms: tanezumab 20 mg SC or matching placebo SC, each administered in addition to background opioids. Subjects who had been randomized to the 10 mg dose treatment arm and who were in the double-blind treatment period at the time of implementation of Amendment 3 were administered 20 mg for any remaining doses.

## STATISTICAL METHODS

The primary efficacy endpoint is the change from Baseline to Week 8 in the average daily pain intensity in the index bone metastasis cancer pain site measured by the 11 point pain intensity Numerical Rating Scale (NRS) where scores range from 0-10. Baseline is defined as the mean average daily pain NRS score during the Baseline Assessment Period prior to randomization. The Week 8 pain intensity value is the mean of the daily average pain intensity scores for the 7 days prior to the Week 8 visit.

The primary efficacy endpoint will be analyzed using an analysis of covariance (ANCOVA) model, with model terms for Baseline score, the stratification variables, Baseline opioid use, region and treatment group. The stratification variables are (i) tumor aggressiveness (assessed by Eastern Cooperative Group [ECOG] performance status and (ii) presence/absence of concomitant anticancer treatment (eg, chemotherapy or hormonal therapy or anti-hormonal therapy).

The primary analysis of the primary endpoint will use multiple imputation for missing data, to account for uncertainty around the subject response. The basis for imputing missing values will be dependent on the reasons for missing data. Refer to Section 9.2 for details.

Data from subjects initially randomized to the tanezumab 10 mg treatment group will be summarized but not included in analyses of efficacy. A Group Sequential Design with a single interim analysis will be used for the assessment of futility and of efficacy of the primary efficacy parameter.

The interim analysis will be performed when at least 50% (36 from each treatment group) of subjects have completed or discontinued prior to Week 8. Based on current enrollment, it is expected that the interim analysis will include approximately 36 to 45 subjects per treatment group.

Based on data from the previous cancer pain study (A4091003), and not accounting for the assessment of futility and efficacy at the interim analysis, a sample size of approximately 72 subjects per treatment group is required to achieve 85% power to demonstrate statistical significance (using the 2-sided 5% significance level), in the treatment comparison of tanezumab 20 mg + opioid versus placebo + opioid. Taking into account for the assessment of non-binding futility and efficacy at the interim analysis, the same sample size is expected to achieve 80 to 85% power.

**EXTERNAL ADJUDICATION COMMITTEE**

A blinded Adjudication Committee consisting of external experts in orthopedic surgery, rheumatology, orthopedic pathology, or radiology with expertise in subjects with end stage osteoarthritis and osteonecrosis will be convened. The Adjudication Committee will be asked to review all joint-related safety events resulting in total joint replacement and/or discontinuation from the study as well as adverse events reported as osteonecrosis, rapidly progressive osteoarthritis, or other events suggestive of abnormal joint destruction. The Adjudication Committee will have written operating procedures and a Charter, including a specific description of the scope of their responsibilities.

**EXTERNAL DATA MONITORING COMMITTEE**

An independent, External Data Monitoring Committee (E-DMC) has been instituted for the tanezumab clinical program. This committee will be composed of at least one rheumatologist, neurologist, statistician, and epidemiologist. The E-DMC will review unblinded safety data including (but not limited to) adverse events and serious adverse events on a regular basis throughout the trial. The E-DMC will have written operating procedures and a Charter, including a specific description of the scope of their responsibilities.

## SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the subject.

**Table 1. Pre-Treatment, Double-Blind & Safety Follow-Up Schedule of Activities**

| | Pre-Treatment Period | | Double-Blind Period | | | | | Safety Follow-Up Period | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screen[b] | Baseline Assessment Period[b] | Baseline Dose[c] | Weeks 2, 4 | Weeks 8, 16 | Weeks 12, 20 | Week 24 | Week 28 | Week 32 | Weeks 36, 40[s], 44 | Week 48[r] |
| Study Day (± X day window) | Day -37 to Day -6 | Day -5 to Day -1 | Day 1 | Days 15, 29 (±3) | Days 57, 113 (±3) | Day 85(±3) Day 141(±5) | Day 169 (±5) | Day 197 (±5) | Day 225 (±7) | Days 253, 281, 309 (±7) | Day 337 (±7) |
| Visit | | | Dosing[*] | Clinic[*] | Dosing[*] | Phone contacts | End of Treatment[*] | Phone Contact | Safety f/u Clinic[*] | Phone Contacts[s] | End of Study[*] |
| Informed Consent | X | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | | X[†] | | | | | | | | |
| Cancer History[d] | X | | | | | | | | | | |
| General and Musculo-skeletal Specific Medical History and Prior/Current Medication Use[e] | X | | | | | | | | | | |
| Primary Diagnosis/ Demographics | X | | | | | | | | | | |
| Smoking /Female Hormonal Status/Alcohol Use | X | | | | | | | | | | |
| General Physical Exam | X | | | | | | X | | | | X |
| Musculoskeletal Assessment[e] | X | | | | X Japan only | | X Japan only | | X Japan only | | X Japan only |

| | Pre-Treatment Period | | Double-Blind Period | | | | | Safety Follow-Up Period | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screen[b] | Baseline Assessment Period[b] | Baseline Dose[c] | Weeks 2, 4 | Weeks 8, 16 | Weeks 12, 20 | Week 24 | Week 28 | Week 32 | Weeks 36, 40[s], 44 | Week 48[r] |
| Study Day (± X day window) | Day -37 to Day -6 | Day -5 to Day -1 | Day 1 | Days 15, 29 (±3) | Days 57, 113 (±3) | Day 85(±3) Day 141(±5) | Day 169 (±5) | Day 197 (±5) | Day 225 (±7) | Days 253, 281, 309 (±7) | Day 337 (±7) |
| Visit | | | Dosing[*] | Clinic[*] | Dosing[*] | Phone contacts | End of Treatment[*] | Phone Contact | Safety f/u Clinic[*] | Phone Contacts[s] | End of Study[*] |
| Imaging confirmation of bone metastasis[f] | X | | | | | | | | | | |
| Pain Scores at cancer pain sites via IRT[a] | X | | | | | | | | | | |
| Confirm index and non-index cancer pain sites | X | | | | | | | | | | |
| CCI | | | | | | | | | | | |
| Vital Signs (BP[a],HR[a]) | X | | X[†] | X | X | | X | | X | | X |
| Weight/Height/BMI[h] | X | | | | | | | | | | X[t] |
| Orthostatic BP testing | X | | X[†] | | X | | X | | | | X |
| Electrocardiogram (ECG 12-lead) | X | | | | | | X | | | | X |
| ECOG Performance Score | X | | | | | | X | | | | X |
| **Subject Reported Assessments Completed at Study Visits via IRT[i]** | | | | | | | | | | | |
| CCI | | | | | | | | | | | |
| Opioid Related Symptom Distress Scale (OR-SDS) | | | X[†] | X | X | | X | | | | |
| Patient Global Assessment (PGA) of Cancer Pain | X | | X[†] | X | X | | X | | | | |
| CCI | | | | | | | | | | | |
| Survey of Autonomic Symptoms (SAS) | X | | | | | | X | | | | X |
| **Laboratory** | | | | | | | | | | | |
| Hepatitis Screen: Hepatitis B & Hepatitis C | X | | | | | | | | | | |
| HIV test | X | | | | | | | | | | |

| | Pre-Treatment Period | | Double-Blind Period | | | | | Safety Follow-Up Period | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screen[b] | Baseline Assessment Period[b] | Baseline Dose[c] | Weeks 2, 4 | Weeks 8, 16 | Weeks 12, 20 | Week 24 | Week 28 | Week 32 | Weeks 36, 40[s], 44 | Week 48[r] |
| Study Day (± X day window) | Day -37 to Day -6 | Day -5 to Day -1 | Day 1 | Days 15, 29 (±3) | Days 57, 113 (±3) | Day 85(±3) Day 141(±5) | Day 169 (±5) | Day 197 (±5) | Day 225 (±7) | Days 253, 281, 309 (±7) | Day 337 (±7) |
| Visit | | | Dosing* | Clinic* | Dosing* | Phone contacts | End of Treatment* | Phone Contact | Safety f/u Clinic* | Phone Contacts[s] | End of Study* |
| Urine Toxicology screen | X | | | | | | | | | | |
| Hemoglobin A1C | X | | | | | | | | | | |
| Serum FSH Test[j] | X | | | | | | | | | | |
| Serum/Urine Pregnancy Test[j] | X | | X[f] | | X | | X | | X | | |
| Hematology | X | | X | | Week 16 | | | | X | | X |
| Blood Chemistry | X | | X | | Week 16 | | | | X | | X |
| PT/PTT[a] | X | | X | | Week 16 | | | | X | | X |
| Urinalysis | X | | | | | | | | | | |
| Serum and Plasma Retention Samples | | | X | | Week 16 | | X | | X | | |
| CCI [redacted] | | | [redacted] | | [redacted] | | [redacted] | | | | [redacted] |
| [redacted] | | | [redacted] | | [redacted] | | | | | | |
| Serum Anti-Drug Antibody (ADA)[k] | | | X | | Week 8 | | X | | | | X |
| CCI [redacted] | | | [redacted] | | [redacted] | | [redacted] | | [redacted] | | [redacted] |
| [redacted] | | | [redacted] | | | | | | | | |
| **Other Activities Initiated at the Screening visit** | | | | | | | | | | | |
| Instruct female subjects of childbearing potential of contraceptive requirements | X | | | | | | | | | | |
| X-ray of major joints and any other at risk joint | X | | | | Week 16 Japan only X[t] | | X | | | | X |

| | Pre-Treatment Period | | Double-Blind Period | | | | | Safety Follow-Up Period | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screen[b] | Baseline Assessment Period[b] | Baseline Dose[c] | Weeks 2, 4 | Weeks 8, 16 | Weeks 12, 20 | Week 24 | Week 28 | Week 32 | Weeks 36, 40[s], 44 | Week 48[r] |
| Study Day (± X day window) | Day -37 to Day -6 | Day -5 to Day -1 | Day 1 | Days 15, 29 (±3) | Days 57, 113 (±3) | Day 85(±3) Day 141(±5) | Day 169 (±5) | Day 197 (±5) | Day 225 (±7) | Days 253, 281, 309 (±7) | Day 337 (±7) |
| Visit | | | Dosing[*] | Clinic[*] | Dosing[*] | Phone contacts | End of Treatment[*] | Phone Contact | Safety f/u Clinic[*] | Phone Contacts[s] | End of Study[*] |
| Discontinue Concomitant NSAID[a] Pain Medication | X | | | | | | | | | | |
| Adjust opioid regimen[l] | X | X | | | ----------X---------- | | | | | | |
| Dispense IRT diary; Instruct subject on use of IRT diary | X | | | | | | | | | | |
| **Subject Daily/Weekly Assessments (via IRT)[m]** | | | | | | | | | | | |
| Average and Worst Cancer Pain (NRS[a]) | ----------X---------- | | | | | ----------X---------- | | | | | |
| Background opioid use | ----------X---------- | | | | | ----------X---------- | | | | | |
| Concomitant NSAID use | | | ----------X---------- | | | | | | | | |
| Assessment of pain in major joints (NRS) | ----------X---------- | | | | | | | | | | |
| **Randomization and Study Treatment** | | | | | | | | | | | |
| Confirm Randomization Criteria have been met[m] | | X | X[†] | | | | | | | | |
| Randomization | | | X | | | | | | | | |
| SC Study Medication Administered | | | X | | X | | | | | | |
| **Other Assessments/Procedures Conducted at Screening, BAP and Study Visits** | | | | | | | | | | | |
| Adverse event assessment | | | X[†] | X | X | X | X | X | X | X[s] | X |
| Review concomitant medication | | | X[†] | X | X | X | X | X | X | X[s] | X |
| Review subject compliance with IRT (subject diary)[o] | X | X | X[†] | X | X | X | X | X | X | X[s] | X |
| Review IRT (Subject diary) entries[o] | X | X | X[†] | X | X | X | X | X | X | X[s] | X |
| Review Contraceptive Requirements[p] | | | X | X | X | X | X | X | X | | |

| | Pre-Treatment Period | | Double-Blind Period | | | | | Safety Follow-Up Period | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screen[b] | Baseline Assessment Period[b] | Baseline Dose[c] | Weeks 2, 4 | Weeks 8, 16 | Weeks 12, 20 | Week 24 | Week 28 | Week 32 | Weeks 36, 40[s], 44 | Week 48[r] |
| Study Day (± X day window) | Day -37 to Day -6 | Day -5 to Day -1 | Day 1 | Days 15, 29 (±3) | Days 57, 113 (±3) | Day 85(±3) Day 141(±5) | Day 169 (±5) | Day 197 (±5) | Day 225 (±7) | Days 253, 281, 309 (±7) | Day 337 (±7) |
| Visit | | | Dosing* | Clinic* | Dosing* | Phone contacts | End of Treatment* | Phone Contact | Safety f/u Clinic* | Phone Contacts[s] | End of Study* |
| Standard of care treatment (except NSAIDs or intra-articular corticosteroids) if needed[q] | | | | | ----------X---------- | | | | | | |
| Standard of care treatment with NSAIDs or intra-articular corticosteroids if needed[u] | | | | | | | | | ----------X---------- | | |

| | Pre-Treatment Period | | Double-Blind Period | | | | | Safety Follow-Up Period | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screen[b] | Baseline Assessment Period[b] | Baseline Dose[c] | Weeks 2, 4 | Weeks 8, 16 | Weeks 12, 20 | Week 24 | Week 28 | Week 32 | Weeks 36, 40[s], 44 | Week 48[r] |
| Study Day (± X day window) | Day -37 to Day -6 | Day -5 to Day -1 | Day 1 | Days 15, 29 (±3) | Days 57, 113 (±3) | Day 85(±3) Day 141(±5) | Day 169 (±5) | Day 197 (±5) | Day 225 (±7) | Days 253, 281, 309 (±7) | Day 337 (±7) |
| Visit | | | Dosing* | Clinic* | Dosing* | Phone contacts | End of Treatment* | Phone Contact | Safety f/u Clinic* | Phone Contacts[s] | End of Study* |

* = These visits are performed on site/in clinic review.
† = Indicates activities to be performed prior to randomization at the Baseline visit.

a. Abbreviations: BMI: Body Mass index; BP (blood pressure); HR: heart rate; IRT, interactive response technology (refers to web-based, phone-based or electronic modes of data capture); NRS: Numerical rating scale; NSAID, non-steroidal anti-inflammatory drug; PT/PTT, prothrombin time/partial thromboplastin time.
b. The Screening Period lasts 1-32 days, allowing for Screening eligibility assessments, washout of prohibited medications and opioid dose optimization prior to the 5-day Baseline Assessment Period.(BAP) Refer to Section 6 for further details of Screening activities and the order in which study procedures should be conducted.
c. Pre-randomization Baseline study procedures indicated with "X†" should be performed prior to randomization. Other Baseline study procedures may be performed either prior to or after randomization but prior to dosing (Day 1). Study medication administration (Dosing) can only be done after randomization.
d. Cancer history consists of primary diagnosis, date of initial diagnosis, date of initial bone metastasis, treatment history.
e. Details of the comprehensive musculoskeletal medical history and musculoskeletal physical exam are described in Section 7.3.3.
f. Confirmation of metastasis in the 120 days prior to Screening in accordance with local standard of care eg,via MRI, CT, PET-CT, or bone scan.
CCI [redacted]
h. Only body weight is collected at Week 48.
i. CCI [redacted] OR-SDS, CCI [redacted] and PGA of Cancer Pain are administered via IRT at the clinic. Subjects should be thoroughly instructed on completion of the scales/instruments and no coaching or other interpretative assistance should be given to subjects during completion of these questionnaires.
j. FSH testing in female subjects as described in Section 7.3.4.4. Serum and urine pregnancy testing are described in Section 7.3.4.3. For female subjects of childbearing potential, urine pregnancy test must be confirmed as negative prior to dosing at dosing visits.
k. At dosing visits, samples for ADA, CCI [redacted] should be obtained pre-dose. CCI [redacted]
l. Opioid regimen dose adjustment if needed (via telephone contact or unscheduled clinic visit); Refer to Sections 6.1.1.2.4 and 6.2.2.1. From Day 1 to Week 8, the background opioid total daily dose (TDD) should not exceed 10% over the TDD established during the Baseline Assessment Period. Opioid regimen can be liberalized starting at Week 8 and adjustments made up or down according to accepted clinical guidelines. Refer to Sections 6.1.1.2.4 and 6.2.2.1.

| | Pre-Treatment Period | | Double-Blind Period | | | | | Safety Follow-Up Period | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screen[b] | Baseline Assessment Period[b] | Baseline Dose[c] | Weeks 2, 4 | Weeks 8, 16 | Weeks 12, 20 | Week 24 | Week 28 | Week 32 | Weeks 36, 40[s], 44 | Week 48[r] |
| Study Day (± X day window) | Day -37 to Day -6 | Day -5 to Day -1 | Day 1 | Days 15, 29 (±3) | Days 57, 113 (±3) | Day 85(±3) Day 141(±5) | Day 169 (±5) | Day 197 (±5) | Day 225 (±7) | Days 253, 281, 309 (±7) | Day 337 (±7) |
| Visit | | | Dosing* | Clinic* | Dosing* | Phone contacts | End of Treatment* | Phone Contact | Safety f/u Clinic* | Phone Contacts[s] | End of Study* |

m. Assessment of randomization criteria includes (but is not limited to) assessment of successful completion of the Baseline Assessment Period (BAP) and radiographic confirmation of eligibility based on central reader assessment; Refer to Section 4.3.

n. IRT (subject diary). Subjects will enter pain scores at index metastasis site and background opioid use (ATC and IR) daily from Screening to Week 8 then weekly until Week 24. Background opioid total daily doses (TDD) will be calculated from the ATC and IR entries. For bone metastasis pain at non-index site(s) average and worst pain scores are collected weekly from Screening to Week 24. Assessment of pain in major joints is collected weekly from Screening to Week 48 (End of Study visit). NSAID use is collected weekly from Baseline to Week 48. Refer to Section 7.1 for details.

o. Compliance with IRT assessments is to be reviewed during the Screening period and at each study visit, including at Phone visits. Cancer pain scores, joint pain scores, opioid use and NSAID medication use reported by the subject should also be reviewed for potential needed actions (eg, as described in Sections 5.8.1, 5.8.1.2.1, 6.1.1.2.4, 6.1.2, 6.2.1.1, 6.2.2.1, 6.4, 7.4.4); Refer to Section 7.1 for IRT assessment details.

p. Female subjects of childbearing potential are instructed on the contraceptive requirements at Screening and then reminded of these requirements at subsequent visits up to when 16 weeks (112 days) have elapsed after the last dose was administered. Contraceptive requirements are described in Section 4.4.

q. If needed, following completion of the Week 8 visit, standard of care treatment (as described in Section 5.8.2.5) may be initiated (with the exception of NSAIDs or intra-articular corticosteroids), and usage recorded on the concomitant medication CRF.

r. Subjects discontinuing the study at their request or at the decision of the investigator prior to Week 24 should be withdrawn from treatment and begin the 24-week Early Termination Follow-Up period described in Section 6.4. The follow-up period for subjects who terminate early includes 3 visits as described in Section 6.4.1). Subjects who undergo joint replacement will be followed for 24 weeks after the procedure as described in Appendix 16.

s. In Japan only, subjects will attend the clinic for this visit at Week 40.

t. In Japan only, confirmation of continued radiographic eligibility from the Central Reader is required before Week 16 dosing. The X-rays (knees, hips and shoulders, and any other major joint imaged at Screening or at-risk joint identified during the study period) may be obtained up to 7 – 21 days before the Week 16 visit (Week 14 ± 7 days).

u. Treatment with NSAIDs or intra-articular corticosteroids may be initiated 16 weeks after administration of the last dose of study medication.

**Table 2. Early Termination Schedule of Activities[a]**

| Protocol Activities | As soon as possible after determining subject will be discontinued from study | Early Termination Visit 1 | Early Termination Telephone Contact 1 | Early Termination Visit 2 | Early Termination Telephone Contact 2 | Early Termination Visit 3 |
|---|---|---|---|---|---|---|
| | | ~8 Weeks after last SC dose | ~12 Weeks after last SC dose | ~16 Weeks after last SC dose | ~20 Weeks after last SC dose | ~24 Weeks after last SC dose |
| X-rays of major joints and any other at risk joints[b] | X | | | | | X |
| General Physical Examination | | X | | | | X |
| Musculoskeletal Physical Examination | | X<br>Japan only | | X<br>Japan only | | X<br>Japan only |
| CCI | | | | | | |
| Vital Signs (BP, HR) | | X | | X | | X |
| Orthostatic Blood Pressure (supine/standing) | | X | | | | X |
| Body Weight | | X | | | | X |
| ECG 12-lead | | X | | | | X |
| ECOG Performance Score | | X | | | | X |
| **Subject Reported Assessments Completed at Study Visits** | | | | | | |
| CCI | | | | | | |
| OR-SDS[e] | | X | | | | |
| PGA of Cancer Pain | | X | | | | |
| CCI | | | | | | |
| CCI | | | | | | |
| **Laboratory** | | | | | | |
| Serum Pregnancy Test | | X | | X | | X[c] |
| Hematology | | | | X | | X |
| Blood Chemistry | | | | X | | X |
| PT/PTT | | | | X | | X |
| Serum and Plasma Retention Samples | | X | | X | | |
| CCI | | | | | | |
| | | | | | | |

| Protocol Activities | As soon as possible after determining subject will be discontinued from study | Early Termination Visit 1 | Early Termination Telephone Contact 1 | Early Termination Visit 2 | Early Termination Telephone Contact 2 | Early Termination Visit 3 |
|---|---|---|---|---|---|---|
| | | ~8 Weeks after last SC dose | ~12 Weeks after last SC dose | ~16 Weeks after last SC dose | ~20 Weeks after last SC dose | ~24 Weeks after last SC dose |
| Serum ADA | | X | | X | | X |
| CCI [redacted] | | [redacted] | | [redacted] | | [redacted] |
| **Subject Weekly Assessments (IRT subject diary)[d]** | | | | | | |
| Assessment of Cancer Pain (NRS) | ----------X---------- | | | | | |
| Opioid use | ----------X---------- | | | | | |
| Joint Pain Assessment | ----------X---------- | | | | | |
| NSAID use | ----------X---------- | | | | | |
| **Other Assessments/Procedures Conducted at Study Visits** | | | | | | |
| Adverse event assessment | | X | X | X | X | X |
| Review concomitant medication | | X | X | X | X | X |
| Review subject compliance with IRT (subject diary) | | X | X | X | X | |
| Review IRT (Subject diary) entries | | X | X | X | X | X |
| Reminder of contraceptive requirements[e] | X | X | X | X | | |
| Liberalize oral opioid regimen if needed[f] | ----------X---------- | | | | | |
| Begin other standard of care treatment (except NSAIDs or intra-articular corticosteroids) if needed[f] | ----------X---------- | | | | | |

| Protocol Activities | As soon as possible after determining subject will be discontinued from study | Early Termination Visit 1 | Early Termination Telephone Contact 1 | Early Termination Visit 2 | Early Termination Telephone Contact 2 | Early Termination Visit 3 |
|---|---|---|---|---|---|---|
| | | ~8 Weeks after last SC dose | ~12 Weeks after last SC dose | ~16 Weeks after last SC dose | ~20 Weeks after last SC dose | ~24 Weeks after last SC dose |

a. Subjects discontinuing the study at their request or at the decision of the investigator prior to Week 24 should be withdrawn from treatment and begin the 24-week Early Termination Follow-Up period described in Section 6.4. Subjects who undergo total joint replacement will be followed for 24 weeks after the procedure as described in Appendix 16.
b. X-rays of major joints (each hip, knee and shoulder) and other at risk major joints identified during the study (see Section 7.3.9) are to be performed as soon as possible following a decision to withdraw a subject from the study is made, provided at least 30 days have passed since the last set of x-rays were collected. If subject discontinues at a study visit, this may be on the same day the Early Termination 1 visit is conducted.
c. A serum pregnancy test at Early Termination Visit 3 is not necessary if it was previously obtained at Early Termination Visit 2 (16 weeks after the last SC dose).
d. Subjects will be asked to continue entering cancer pain scores and opioid treatment weekly until Early Termination Visit 2 which is the visit that occurs after complete washout of tanezumab (5 half-lives), and to enter joint pain scores and NSAID use weekly until Early Termination Visit 3.
e. Female subjects of childbearing potential are instructed on the contraceptive requirements at Screening and then reminded of these requirements at subsequent visits up to when 16 weeks (at least 112 days) have elapsed after the last dose was administered. Contraceptive requirements are described in Section 4.4.
f. If needed, opioid regimen may be liberalized, or standard of care treatment (as described in Section 5.8.2.5) may be initiated, as soon as the site is made aware of the subject's decision to discontinue. NSAIDs or intra-articular corticosteroids should not be re-instituted until at least 16 weeks (112 days) have elapsed since administration of the last dose of study medication.

# 1. INTRODUCTION

## 1.1. Mechanism of Action/Indication

Tanezumab (PF-04383119, formerly RN624) is an anti-nerve growth factor monoclonal antibody under development for the management of cancer pain.

## 1.2. Background and Rationale

### 1.2.1. Role of Nerve Growth Factor in the Modulation of Pain

During mammalian development, nerve growth factor (NGF) is required for the survival and growth of several populations of neurons. In adults, the effect of NGF signaling shifts from the regulation of neuronal survival to the regulation of neuronal phenotype and function. The role of NGF in the adult mammal appears to principally be as a modulator of nociceptive neuronal activity and modulation of the pain response.[6,7] Many non-clinical studies employing a variety of antibodies to NGF or IgG fusion proteins coupled to tropomyosin receptor kinase A (trkA; one of the primary receptors for NGF) have demonstrated that blocking NGF bioactivity normalizes pain sensitivity, particularly in states of allodynia and hypersensitivity, following a variety of insults such as Freund's adjuvant, carrageenan, surgical incision or administration of cytokines.[7,8] Together these observations suggest that NGF may play a role in pain secondary to inflammation or injury.

### 1.2.2. Description of Investigational Product

Tanezumab is a humanized immunoglobulin G Type 2 ($IgG_2$) monoclonal antibody, derived from a murine precursor with a mutation in the Fc portion of the antibody to decrease its ability to activate complement or to support antibody dependent cell-mediated cytotoxicity.[9,10] Tanezumab is highly potent in sequestering NGF and preventing interaction with the trkA or p75 receptors.[2]

### 1.2.3. Overview of Bone Metastasis and Metastatic Bone Pain

With improved medical treatment of many cancers, patients are living longer, which places them at increased risk to develop metastatic disease. The skeleton is the third most common target of metastatic cancer and can be the one of the earliest sites affected.[11]

Cancers of the breast and prostate are particularly likely to spread to bone; about 70% of patients who die from these diseases have evidence of skeletal involvement at autopsy. Carcinomas of the thyroid, kidney, and bronchus also often cause bone metastasis with a postmortem incidence of 30% to 40%, but, by contrast, tumors of the gastrointestinal tract do so rarely, affecting only about 5% of patients dying from these malignancies. Given the high prevalence of carcinomas of the breast, prostate, and lung, it is estimated that these cancers probably account for more than 80% of cases of metastatic bone disease.[12]

For many patients, metastatic bone cancer is a chronic condition, with survival from the time of diagnosis varying significantly among the various tumor types. For bone metastasis from prostate and breast and in multiple myeloma, median survival time from diagnosis is measurable in years. For advanced lung cancer, it is usually measured in months.[13]

Pain associated with cancer is a substantial problem that negatively impacts patients' quality of life, especially as emerging therapies directed against the underlying cancer have begun to prolong patient survival. While pain can result from a number of causes, bone metastasis is the most common cause of cancer pain, occurring in 60 to 84% of patients[14,15] More than 70% of patients with bone metastasis report moderate to severe pain that has a significant impact on their functional status and quality of life.[14,16,17]

Treatment of bone metastasis is primarily palliative, in order to relieve pain, prevent development of pathological fractures and improve mobility and function.[18,19] Conventional treatment uses a multidisciplinary approach including local radiotherapy to the painful area along with systemic treatment (hormone therapy or chemotherapy or radioisotopes) and supportive care such as analgesic therapy, corticosteroids and bisphosphonates.[20 21] Unfortunately, chronic pain resulting from bone metastasis is relatively resistant to analgesics; therefore, its management remains a challenge for clinicians.[16,18]

The basic approach to cancer pain treatment was designed by the World Health Organization (WHO) in 1986[22] and was subsequently revised in 1996.[23] This approach uses a 3-step analgesic ladder in which patients begin treatment with non-opioids and move up the ladder to mild opioids and finally to strong opioids if their pain is not sufficiently controlled by analgesic treatments in the first step(s) of the ladder. Since the initial WHO publication, other groups have issued guidelines for management of cancer.[24,25,26,27] Overall there has been increasing use of opioids for management of cancer pain and opioids remain the mainstay for treatment of moderate to severe cancer pain.

The use of non-steroidal anti-inflammatory drugs (NSAIDs) in cancer-related bone pain has been questioned since the evidence in the medical literature is poor. In addition, there is a possibility that NSAIDs and cyclooxygenase (COX)-2 inhibitors could affect bone health by inhibiting COX enzymes which reduce synthesis of prostaglandins.[18]

Recent investigations have shown that opioids may impair bone metabolism and chronic opioid users have an increased risk of fractures.[18,28] In addition, recent publications seem to hint that opioids may have a possible role in tumor progression.[29]

Despite the widespread use of opioids, results of a recent systematic review current literature for randomized controlled trials of opioids for management of cancer pain noted the level of evidence for pain relief was only fair for transdermal fentanyl and was poor for morphine, tramadol, oxycodone, methadone and codeine.[30] A 10-year validation study of the World Health Organization analgesic ladder in 1995[31] suggested that 76% of patients could achieve good pain relief using the principles of the ladder, a further 12% achieved satisfactory efficacy and 12% had inadequate efficacy. Unfortunately, subsequent studies suggest that these results are not achieved in clinical practice and that much cancer pain continues to be poorly controlled.[32]

The issues described above support the need for better treatments for patients suffering from metastatic bone pain.

### 1.2.4. Overview of Clinical Studies

A total of 32 clinical studies involving over 11,000 subjects have been conducted with tanezumab as of September 2013. Most of these studies were conducted in subjects with osteoarthritis of the knee or hip. A total of 17 clinical studies (4 Phase 2 studies and 13 Phase 3 studies [10 controlled]) were initiated to provide evidence of efficacy and safety of tanezumab with IV (intravenous) or SC administration for the relief of the signs and symptoms of osteoarthritis alone or in combination with NSAIDs. In addition to the osteoarthritis studies, 11 Phase 1/2 studies were conducted to examine the efficacy and safety of tanezumab in other musculoskeletal, neuropathic, and visceral chronic pain conditions, and 2 Phase 2 studies were conducted in cancer subjects with metastatic bone pain. In these studies, tanezumab was administered by IV or SC administration every 8 weeks at fixed doses ranging from 1 mg to 20 mg or equivalent body-weight adjusted doses.[2]

Robust efficacy was demonstrated in osteoarthritis and chronic low back pain studies. Efficacy and safety results observed in non-cancer pain populations are described in the tanezumab investigator brochure,[2] in publically-available documents prepared for the United States (US) Food and Drug Administration (FDA) Arthritis Advisory Committee meeting on March 12, 2012[3,4,5] and in external publications of individual studies.[37,38,39,40,41,42]

#### 1.2.4.1. Efficacy in Cancer Pain Studies

##### 1.2.4.1.1. Study A4091003

The efficacy of tanezumab in subjects with painful bone metastasis has been evaluated in Study A4091003, which was a randomized, double-blind, placebo-controlled, parallel group study in subjects with cancer pain due to bone metastasis who were receiving background treatment with opioids.[43] In Study A4091003, a total of 59 subjects were treated with either a single IV dose of tanezumab 10 mg (N=29) or placebo (N=30).

A positive outcome for the primary efficacy endpoint for Study A4091003 (ie, the change from Baseline to Week 6 in the daily average pain intensity) was not achieved. Although the mean decrease from Baseline in the tanezumab 10 mg IV treatment group was numerically greater than that for the placebo treatment group, the difference was estimated to be -0.26 (95% CI: -1.18, 0.66) and was not statistically significant (p=0.569).

Post-hoc subgroup analyses indicated that subjects with high Baseline pain scores (>5) in combination with low total weekly opioid use (≤60.5 morphine equivalents) may yield the largest treatment difference from placebo. In this subgroup, the estimated treatment difference between tanezumab 10 mg and placebo was -2.72 (95% CI: -5.11, -0.33), and this difference was statistically significant (p=0.027). In another subgroup analysis, subjects with Baseline pain scores >5 (irrespective of Baseline opioid use) had an estimated treatment difference between tanezumab 10 mg and placebo of -1.67 (95% CI: -3.41, 0.08) with p=0.061 when using Baseline Observation Carried Forward (BOCF) imputation at Week 8. Refer to the tanezumab investigator brochure for additional details.[2]

#### 1.2.4.1.2. Study A4091029

Study A4091029 was a safety extension study designed to investigate the safety and efficacy of tanezumab 10 mg intravenous (IV) in subjects with pain due to bone metastasis who had been randomized and treated in the double-blind parent Study A4091003 and who wished to receive open-label tanezumab therapy.

The change from Study A4091003 Baseline in average pain was maintained up to Week 24 in A4091029 for all subjects. For the 6 subjects who received placebo in Study A4091003, the average pain score in A4091029 subsequently worsened from Week 24 to Week 40 (back to the Study A4091003 Baseline pain level). However for subjects who received tanezumab 10 mg in Study A4091003, the improvement in average pain was further maintained to Week 40 of Study A4091029.[44]

### 1.2.4.2. Safety in Cancer Pain Studies

#### 1.2.4.2.1. Study A4091003

In Study A4091003 (N=59), the incidence of subjects with adverse events was comparable between the tanezumab 10 mg treatment group (62.1%) and in the placebo treatment group (60.0%). One subject in the tanezumab 10 mg treatment group (disease progression; 3.3%) and one subject in the placebo treatment group (embolic stroke; 3.4%) discontinued from the study due to an adverse event. The incidence of serious adverse events was higher in the tanezumab 10 mg treatment group (24.1%) compared with the placebo treatment group (13.3%). Three subjects in total died during the study, 2 (6.9%) in tanezumab 10 mg and 1 (3.3%) in placebo treated subjects. The causes of death for subjects in the tanezumab 10 mg treatment group were disease progression and acute cardiac failure and for the subject in the placebo treatment group the cause of death was disease progression. None of the deaths were considered by the investigator to be related to study medication. Refer to the tanezumab Investigator Brochure for additional details.[2]

#### 1.2.4.2.2. Study A4091029

In A4091029,[44] (N=41) the incidence of adverse events was comparable to (though marginally greater than) the adverse event incidence for tanezumab-treated subjects in the parent Study A4091003.[43] Nausea was the most common adverse event and is a well-known side effect of opiates which most of the subjects were taking as background analgesia and thus that adverse event was likely caused by the opiates. In addition, the incidence of serious adverse events (including death) and discontinuations due to adverse events was greater in A4091029 than in A4091003, and reflected the progression of the underlying cancer. In A4091029 there were no reported events of osteonecrosis or total joint replacements.[44] Refer to the tanezumab Investigator Brochure for additional details.[2]

### 1.2.5. Dose Selection Rationale

In Study A4091003, tanezumab 10 mg administered as a single intravenous infusion in subjects with painful bone metastasis despite background opioid treatment did not demonstrate a significant improvement versus placebo in average daily pain scores at the Week 6 primary endpoint. However, there was evidence of efficacy for tanezumab 10 mg in post-hoc subgroup analyses of subjects with Baseline pain scores >5 and Baseline opioid use

below the median value for the study (60 mg/day in morphine equivalents). Also, in subjects with Baseline pain scores >5 irrespective of Baseline opioid use, a meaningful treatment difference was demonstrated, indicating that it may be possible to demonstrate tanezumab efficacy in subjects with painful bone metastasis under different study conditions.

Within the tanezumab program, there has been a demonstration that different doses of tanezumab may be needed for optimal efficacy, depending on the pain condition under study. For example, tanezumab 10 mg dose levels were needed to achieve comparable levels of efficacy in chronic lower back pain study A4091012 vs 5 mg in Phase 3 osteoarthritis studies. In a small proof of concept study in subjects with painful diabetic neuropathy (A4091031), a single subcutaneous injection of tanezumab 20 mg demonstrated efficacy vs placebo at Week 8. There is no evidence that more frequent dosing would be beneficial in cancer pain compared to other disease states.

The tanezumab 20 mg every 8 weeks dose regimen was studied in Study A4091012. Although it was associated with higher frequencies of adverse events and withdrawals due to adverse events than the lower tanezumab doses, the incidence of serious adverse events was comparable to placebo for all tanezumab doses and tanezumab was considered to be generally safe and well-tolerated in this study. In Study A4091031, tanezumab 20 mg was considered to be generally safe and well tolerated.

Based on the results of the studies noted above there has been precedence for efficacy with the tanezumab 20 mg dose. Because the performance of tanezumab 10 mg in A4091003 was not convincingly robust, the current study will explore the efficacy of tanezumab 20 mg in the population of subjects with painful bone metastasis despite background opioid treatment. Although the primary endpoint is at Week 8, this study has a 24-week double-blind treatment duration to evaluate safety and maintenance of efficacy during 6 months of treatment in this study population.

### 1.2.6. Rationale for Placebo Treatment

The use of a placebo comparator is the gold-standard for assessing efficacy in short-term pain studies. Utilization of placebo as a comparator allows a smaller sample size and thus demonstrates the study objectives of efficacy more efficiently than a study using an active comparator. In addition, the use of a placebo arm is most important when the trial endpoints are subjective measures such as those used in this study, because of the often great variation in the way individuals perceive subject-reported outcomes. This was reported to be particularly relevant for studies involving pain relief, depression, and asthma.[45] In this study SC placebo is used to blind investigators and subjects as to whether or not SC tanezumab has been administered. Although minimal analgesic efficacy is expected from placebo treatment, some placebo-treated subjects may experience a beneficial effect on well-being. Background opioid medication (both around the clock [ATC] and immediate release [IR] opioids) will be provided to all subjects to maintain Baseline pain relief throughout the study.

### 1.2.7. Rationale for Opioid Background

Unfortunately, finding effective analgesia for cancer pain due to bone metastasis is challenging and subjects with bone metastasis frequently require opioid treatment once non-opioids have failed to provide adequate pain relief. In this clinical setting, the use of background opioids allows a comparison of tanezumab vs placebo in a manner that allows determination of efficacy and safety of tanezumab in subjects with metastatic bone pain.

### 1.2.8. Rationale for Population

Bone tissue is richly innervated by NGF- responsive neurons. More than 80% of all sensory nerve fibers that innervate the bone are trkA-positive, whereas only 30% of the sensory nerve fibers innervating skin are trkA-positive.[33]

In addition, studies of prostate tumor cells injected into bone suggest NGF is pathologically elevated in these tumors and that the source of increased NGF release is not tumor cells but rather tumor-associated stromal, inflammatory and immune cells, which frequently account for 10–80% of the cells comprising the tumor mass. NGF released by these cells can induce a 10- to 70-fold increase in density of trkA positive sensory nerve fibers in the bone marrow.[33] Thus, in the presence of NGF-releasing tumor, there is a further enrichment of NGF-responsive neurons in bone.

Preclinical studies of the murine precursor antibody to tanezumab (MAb 911) in both prostate and sarcoma models of bone cancer showed the anti-NGF antibody was more effective than or equivalent to acute morphine therapy in reducing bone cancer pain-related behavior in mice.[34,35]

In summary, the rich innervation of bone by NGF-responsive neurons, pathologic elevation of NGF and NGF-responsive neurons in bone metastasis, preclinical studies demonstrating metastatic bone pain efficacy with MAb 911 and tanezumab clinical study results together provide the rationale to study tanezumab in subjects with metastatic bone pain.

As the pain generated by bone metastasis is thought to have the same pathophysiologic mechanism,[36] the potential effect of tanezumab on metastatic bone pain should be similar, regardless of underlying tumor type.

### 1.2.9. Benefit vs Risk for the Study Population

As noted in Sections 1.2.4.1 and 1.2.8, there is rationale for studying tanezumab in patients with painful bone metastasis based on the biology of bone innervation and bone metastasis, preclinical studies in animals with bone metastasis in which anti-NGF treatment demonstrated analgesia and two Phase 2 clinical tanezumab studies in subjects with painful bone metastasis. The population selected for this study is subjects with moderate to severe cancer pain predominantly due to bone metastasis who have had inadequate pain relief with opioids and who are seeking effective treatment options. The rationale for the choice of this population is to optimize the potential benefit-risk relationship for subjects entering the study by selecting subjects who have cancer pain that is more severe or treatment-resistant and who have limited treatment options remaining.

In Study A4091003, there was some evidence of efficacy of tanezumab 10 mg in this population, but the pre-specified primary efficacy endpoint was not achieved. Therefore, in this study, a higher dose arm (tanezumab 20 mg) is being studied, and is considered to be generally safe and well-tolerated (see Section 1.2.5.).

In order to reduce risk in this population, subjects with symptomatic osteoarthritis of the knees, hips or shoulders will be excluded from participation. Additional risk mitigation measures that have been developed as an outgrowth of the joint-related safety analyses to reduce the risk of rapidly progressive osteoarthritis are included in this study, along with additional assessments of sympathetic nervous system safety.

In addition, exclusion of subjects with poor Eastern Cooperative Oncology Group (ECOG) Performance Status[47] (used as a surrogate measure of tumor aggressiveness), or safety laboratory findings, supports appropriate benefit-risk in this patient population and across tumor types.

Complete information for tanezumab may be found in the Single Reference Safety Document (SRSD), which for this study is the Investigator Brochure.[2]

# 2. STUDY OBJECTIVES AND ENDPOINTS

## 2.1. Objectives

### 2.1.1. Primary Objective

- Demonstrate superior analgesic efficacy of tanezumab 20 mg SC versus matching placebo SC at Week 8 in subjects, with cancer pain predominantly due to bone metastasis, receiving background opioid therapy.

### 2.1.2. Secondary Objective

- Evaluate the safety of tanezumab 20 mg SC versus matching placebo SC in subjects, with cancer pain predominantly due to bone metastasis, receiving background opioid therapy.

## 2.2. Endpoints

### 2.2.1. Primary Endpoint

- Change from Baseline to Week 8 in the daily average pain intensity in the index bone metastasis cancer pain site.

### 2.2.2. Secondary Endpoints

#### 2.2.2.1. Efficacy Measures

- Change from Baseline to Weeks 1, 2, 4, 6, 12, 16 and 24 in the daily average pain intensity NRS score in the index bone metastasis cancer pain site.

- Change from Baseline to Weeks 1, 2, 4, 6, 8, 12, 16 and 24 in the daily worst pain intensity NRS score in the index bone metastasis cancer pain site.

- Change from Baseline to Weeks 1, 2, 4, 6, 8, 12, 16 and 24 in the weekly average pain intensity NRS score in non-index cancer pain sites.

- Change from Baseline to Weeks 1, 2, 4, 6, 8, 12, 16 and 24 in the weekly worst pain intensity NRS score in non-index cancer pain sites.

- Change from Baseline to Weeks 1, 2, 4, 6, 8, 12, 16 and 24 in the daily average pain intensity NRS score in the non-index visceral cancer pain sites.

- Change from Baseline to Weeks 1, 2, 4, 6, 8, 12, 16 and 24 in the daily worst pain intensity NRS score in the non-index visceral cancer pain site.

- [redacted]

- [redacted]

- Response as defined by a ≥30%**,** ≥50%, ≥70%, and ≥90% reduction from Baseline in the daily average and daily worst pain intensity NRS score in the index bone metastasis cancer pain site at Weeks 1, 2, 4, 6, 8, 12, 16 and 24.

- Change from Baseline in Patient's Global Assessment of Cancer Pain at Weeks 2, 4, 8, 16 and 24.

- Response defined as an improvement of ≥2 points in Patient's Global Assessment of Cancer Pain at Weeks 2, 4, 8, 16 and 24.

- [redacted]

- [redacted]

#### 2.2.2.2. Opioid Use and Opioid Adverse Effects Measures

- Average daily total opioid consumption (in mg of morphine equivalent doses) at Weeks 1, 2, 4, 6, 8, 12, 16 and 24.

- Average number of doses of rescue medication required per week at Weeks 1, 2, 4, 6, 8, 12, 16 and 24.

- Change from Baseline in the weekly Opioid-Related Symptom Distress Scale at Weeks 2, 4, 8, 16, and 24.

### 2.2.2.3. Safety Measures

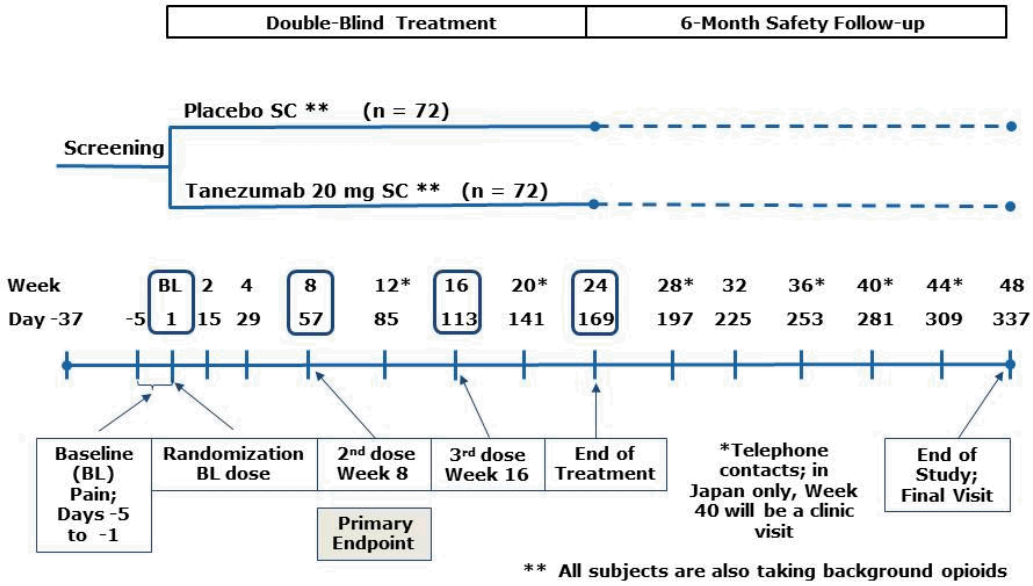
- Adverse events.
- Standard safety assessments (safety laboratory testing [chemistry, hematology], sitting vital signs, ECG [12-lead]).
- Orthostatic (supine/standing) blood pressure assessment.
- Weight measurements.
- Physical examinations.
- Joint safety adjudication outcomes.
- Total joint replacements.
- [redacted]
- [redacted]
- Anti-drug antibody (ADA) assessments.

CCI [redacted]

- [redacted]
- [redacted]
- [redacted]

## 3. STUDY DESIGN

**Figure 1. Study Design**




This is a randomized, double-blind, placebo-controlled, multicenter, parallel-group Phase 3 study in cancer subjects requiring treatment with background opioids for pain due to bone metastasis.

The protocol was initially designed to include 3 treatment groups (tanezumab 20 mg SC, tanezumab 10 mg SC, and placebo), and was amended (Amendment 3) after study start to discontinue the tanezumab 10 mg dose arm. It is estimated that approximately 11 subjects in total were randomized to receive tanezumab 10 mg SC prior to implementation of Amendment 3.

Following implementation of Amendment 3, subjects were randomized in a 1:1 ratio (planned 85 subjects/arm) to one of two treatment arms: tanezumab 20 mg SC or matching placebo SC, each administered in addition to background opioids. Subjects who had been randomized to the 10 mg dose treatment arm and who were in the double-blind treatment period at the time of implementation of Amendment 3 were administered 20 mg for any remaining doses.

In protocol Amendment 4, the sample size has been reduced. A total of 155 subjects will be randomized. This comprises 144 subjects (72/treatment arm) randomized to receive tanezumab 20 mg SC or matching placebo SC plus an estimated 11 subjects previously randomized to receive tanezumab 10 mg SC.

Subjects will receive a total of 3 SC injections, separated by 8 weeks in addition to background opioids administered throughout the study: Treatment groups will include:

1. Placebo SC (matching tanezumab SC) in addition to background opioid therapy.

2. Tanezumab 20 mg SC in addition to background opioid therapy.

The study is designed with a post-randomization duration of 48 weeks and will consist of three periods: Pre-Treatment (up to 37 days), Double-Blind Treatment (24 weeks) and 6-month Safety Follow-Up (24 weeks). The Pre-Treatment Period will include a Screening Period (lasting up to 32 days) with washout of prohibited study medication and stabilization of background opioid regimen prior to a 5-day Baseline Assessment Period.

Confirmation of radiographic eligibility by a central radiologist based on protocol-defined x-rays will take place during the Pre-Treatment period. The study is designed such that post randomization, contacts with subjects are made approximately every 4 weeks through the end of the Safety Follow-Up period. The Double-Blind Treatment Period consists of 6 in-clinic visits (including 3 dosing visits) and 2 phone contact visits. Because of the long half-life of tanezumab (approximately 21 days), the End of Double-Blind Treatment visit takes place 8 weeks after the last dose of SC medication is administered. The Safety Follow-Up period begins with the completion of the End of Treatment visit and includes 4 phone contacts and 2 additional in-clinic visits, with the exception of sites in Japan where 3 phone contacts and 3 additional in-clinic visits will occur. Refer to Section 6 for the procedures to be performed during the study.

Changes from Baseline in pain intensity in the index bone metastasis site and non-index cancer pain sites, along with other measures of efficacy and safety will address the primary and secondary study objectives. Refer to Section 7 for descriptions of the efficacy and safety assessments to be performed during the study.

Stratification variables are (i) tumor aggressiveness (assessed by Eastern Cooperative Group [ECOG] performance status and (ii) presence/absence of concomitant anticancer treatment (eg, chemotherapy or hormonal therapy or anti-hormonal therapy). Stratification by ECOG performance status will balance treatment groups with respect to tumor aggressiveness to minimize imbalances in tumor-specific safety findings. Stratification based on presence/absence of concomitant anticancer treatment will control for potential confounding effects of anticancer treatment on efficacy. Refer to Section 9 for details regarding sample size determination and stratification.

## 4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in this study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

### 4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.

2. Subject is willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

3. Male or female, ≥18 years of age.

4. Weight is ≥40 kg at Screening;

5. Subject has cancer diagnosed as having metastasized to bone or has multiple myeloma.

6. Imaging confirmation of bone metastasis at Screening or within 120 days prior to the Screening visit according to local standard of care (eg, via bone scan, magnetic resonance imaging (MRI), computed tomography (CT) scan, or positron emission tomography-computed tomography (PET-CT) scan).

7. Subject is expected to require daily opioid medication throughout the course of the study.

8. Subject willing to not use prohibited medications (including NSAIDs) throughout the duration of the study (refer to Section 5.8.1 for details regarding prohibited concomitant medications).

9. Average Pain Score ≥5 at Screening for the index bone metastasis cancer pain site (refer to Section 6.1.1).

10. Patient's Global Assessment of Cancer Pain must be "fair", "poor" or "very poor" at Screening.

11. Eastern Cooperative Oncology Group (ECOG) Performance Status Score[47] of 0, 1, or 2 at Screening (refer to Appendix 3).

12. Adequate bone marrow function at Screening (confirmed by a repeat test if needed), as defined by:

    a. Absolute Neutrophil Count (ANC) ≥1,500/$mm^3$ or ≥1.5 x $10^9$/L;

    b. Platelets ≥100,000/$mm^3$ or ≥100 x $10^9$/L;

    c. Hemoglobin ≥9.0 g/dL.

13. Adequate renal function at Screening (confirmed by a repeat test if needed), as defined by:

    a. Estimated glomerular filtration rate ≥30 mL/min as calculated by the Central Laboratory, and

b. Urinary protein <2+ by urine dipstick performed by the Central Laboratory. If dipstick is ≥2+, then 24 hour urinary protein <2 g per 24 hours.

14. Adequate liver function at Screening (confirmed by a repeat test if needed), as defined by:

    a. Total serum bilirubin ≤1.5 x upper limit of normal (ULN);

    b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN (≤5.0 x ULN if there is tumor involvement in the liver);

    c. Alkaline phosphatase ≤5 x ULN.

15. International Normalized Ratio (INR) or prothrombin time (PT) <1.5 x ULN at Screening (confirmed by a repeat test if needed), provided the subject is not being treated with anticoagulant medication. For subjects being treated with anticoagulants, the INR should be within the range recommended for the specific clinical indication.

16. Female subjects of childbearing potential and at risk for pregnancy must agree to use at least one highly effective method of contraception throughout the study and for 112 days (16 weeks) after the last dose of assigned subcutaneous study medication.

17. Female subjects who are not of childbearing potential (ie, must meet at least one of the following criteria):

    - Have undergone documented hysterectomy and/or bilateral oophorectomy;
    - Have medically confirmed ovarian failure; or
    - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and have a serum follicle stimulating hormone (FSH) level confirming the post-menopausal state.

### 4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. The subject's pain is related to an oncologic emergency such as bowel obstruction/perforation, spinal cord compression, epidural metastasis, or fracture or impending fracture of weight bearing bone.

2. The subject has brain metastasis or leptomeningeal metastasis.

3. Presence of hypercalcemia at Screening (confirmed by a repeat test if needed), defined as albumin-corrected serum calcium concentration of ≥12 mg/dL. If

measured albumin is <4.5 gm/dL, corrected calcium (mg/dL) = measured calcium (mg/dL) + 0.8 x (4.5 gm/dL-measured albumin in gm/dL).

4. The subject's pain is primarily classified as neuropathic, visceral or unknown in nature, has resulted from prior cancer therapy, is due to infection or is otherwise not predominantly related to a bone metastasis.

5. Systemic treatment for the primary malignancy or bone metastasis, including chemotherapy, hormonal treatment (eg, gonadotropin-releasing hormone (GnRH) agonists or antagonists), bisphosphonates and denosumab started within 30 days of the first day of the Baseline Assessment Period.

   Chemotherapies associated with peripheral neuropathy (ie, paclitaxel, docetaxel, oxaliplatin, cisplatin, vincristine, thalidomide or bortezomib[48]), are prohibited during study period from 30 days prior to the first day of the Baseline Assessment Period to Week 48.

6. Receipt of radiopharmaceutical treatment or radiotherapy for treatment of bone metastasis within 30 days of the first day of the Baseline Assessment Period. Subjects who are candidates for external beam radiotherapy for painful bone metastasis should not be considered for this study in lieu of external beam radiotherapy.

7. Initiation or unstable dose of concurrent adjuvant analgesics such as single-agent acetaminophen (paracetamol), serotonin norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants, anticonvulsant medication, corticosteroids, or muscle relaxants within 30 days of the start of the Baseline Assessment Period.

8. Diagnosis of osteoarthritis of the knee or hip as defined by the American College of Rheumatology (ACR) combined clinical and radiographic criteria (refer to Appendix 4); Radiographic criteria will be assessed by the Central Reader.

9. Subjects with symptoms and radiographic findings (eg, joint space narrowing, osteophytes) consistent with osteoarthritis in the shoulder.

10. History of significant trauma or surgery to a major joint (eg, hip, knee or shoulder) within one year prior to Screening.

11. A history of osteonecrosis or osteoporotic fracture (ie, a subject with a history of osteoporosis and a minimally traumatic or atraumatic fracture).

12. Radiographic (x-ray) evidence of any of the following conditions as determined by the central radiology reviewer and as defined in the tanezumab program imaging atlas at Screening: 1) rapidly progressive osteoarthritis, 2) atrophic or hypotrophic osteoarthritis, 3) subchondral insufficiency fracture, 4) spontaneous osteonecrosis of the knee (SPONK), 5) osteonecrosis, or 6) pathologic fracture.

**NOTE**:

- Necrosis of the bone secondary to radiotherapy (ie, osteoradionecrosis) and in relation to metastatic disease of the bone (ie, involving the tumor-bone interface) is allowable.

- Vertebral pathologic fracture with less than 50% vertebral body destruction and no spinal canal compromise is allowable.

- A treated (eg, fixation) and resolved pathologic fracture of a non-weight bearing bone (eg, humerus) is allowable if not involving a major joint.

13. Signs and symptoms of clinically significant cardiac disease including but not limited to:

    a. Ischemic cardiac disease (eg, unstable angina, myocardial infarction) in the 6 months prior to Screening;

    b. Surgery or stent placement for coronary artery disease in the 6 months prior to Screening;

    c. New York Heart Association (NYHA) Class III or IV congestive heart failure or known left ventricular dysfunction with ejection fraction ≤35%, cardiomyopathy, myocarditis in the 6 months prior to Screening;

    d. Resting tachycardia (heart rate ≥120) or resting bradycardia (heart rate ≤45) on ECG at Screening;

    e. Any other cardiovascular illness that in the opinion of the investigator would render a subject unsuitable to participate in the study.

14. Subjects who have evidence of orthostatic hypotension based upon replicate orthostatic blood pressure measurements at Screening or at Baseline prior to randomization (refer to Section 7.3.7). If orthostatic blood pressure change cannot be determined (eg, unable to establish a stable supine systolic and diastolic blood pressure) that subject is not eligible for the study.

15. Diagnosis of a transient ischemic attack in the 6 months prior to Screening or diagnosis of stroke with residual deficits (eg, aphasia, substantial motor or sensory deficits), that would preclude completion of required study activities.

16. History, diagnosis, or signs and symptoms of clinically significant neurological disease including but not limited to:

    a. Alzheimer's disease or other types of dementia;

    b. Clinically significant head trauma within the past year;

    c. Peripheral neuropathy or autonomic neuropathy; (Note: Subjects with a stable, chemotherapy-induced peripheral polyneuropathy over the 6 months prior to

Screening will be considered eligible provided they are no longer being treated with chemotherapy associated with peripheral neuropathy (ie, paclitaxel, docetaxel, oxaliplatin, cisplatin, vincristine, thalidomide or bortezomib[48]). Subjects with confirmed cancer-induced neuropathy or paraneoplastic neuropathy should be excluded.

d. Epilepsy or seizure disorder with seizure within 2 years of Screening;

e. Myopathy;

f. Brain or leptomeningeal metastasis.

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18. Subjects with a past history of carpal tunnel syndrome (CTS) with signs or symptoms of CTS in the one year prior to Screening.

19. The subject has a history of significant alcohol, analgesic, or narcotic substance abuse within the six months prior to Screening.

20. Planned surgical procedure during the duration of the study.

21. Subjects considered unfit for surgery, defined as Grade >3 on the American Society of Anesthesiologists (ASA) physical classification system for surgery (refer to Appendix 6) or subjects who would not be willing to undergo joint replacement surgery if required.

22. Subject has known hypersensitivity to opioids or an underlying medical condition contraindicating opioid use.

23. Subject has a history of allergic or anaphylactic reaction to a therapeutic or diagnostic monoclonal antibody or IgG-fusion protein.

24. Previous exposure to exogenous nerve growth factor or to an anti-nerve growth factor antibody.

25. Presence of drugs of abuse (except for opioids or cannabinoids, as allowed per protocol), prescription medications without a valid prescription or other illegal drugs in the urine toxicology screen obtained at Screening.

26. Positive Hepatitis B, Hepatitis C, or Human Immunodeficiency Virus (HIV) tests at Screening indicative of current infection.

27. Subjects who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees directly involved in the conduct of the trial.

28. Participation in other studies involving investigational drug(s) (Phases 1-4) within 30 days (or 90 days for investigational biologics) before Baseline Assessment Period and/or during study participation.

29. Pregnant female subjects; breastfeeding female subjects; female subjects of childbearing potential who are unwilling or unable to use one (1) highly effective method of contraception as outlined in this protocol for the duration of the study and for 112 days (16 weeks) after last dose of investigational product.

30. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

### 4.3. Randomization Criteria

The following criteria must be met to be eligible for randomization:

1. There have been ≤3 IR rescue episodes per day for breakthrough pain from Day -3 to Day -1 during the Baseline Assessment Period.

2. The mean value of the average daily pain scores for the index bone metastasis cancer pain site from Day -5 to Day -1 during the Baseline Assessment Period must be ≥5; Subjects must complete interactive response technology (IRT) pain assessments on at least 3 of the 5 days during the Baseline Assessment Period.

3. There are no intolerable opioid side effects in the judgment of the subject from Day -3 to Day -1 during the Baseline Assessment Period.

4. The Patient's Global Assessment of Cancer Pain must be "fair", "poor" or "very poor" at the Baseline Visit.

5. Radiologic eligibility must have been confirmed by the Central Reader during the Screening Period, Baseline Assessment Period or at the Baseline Visit.

### 4.4. Lifestyle Guidelines

Subjects should maintain their normal daily routine, including stable doses of permitted medications and exercise program. Subjects are also permitted to continue with non-pharmacologic activities (eg, massage, physical therapy) during the trial. Subjects should be cautioned against initiating or altering strenuous exercise regimens during the study as this may influence efficacy and laboratory results. Subjects will be advised to avoid elective surgery (eg, oral surgery) during the course of the study if possible; the study clinician should be contacted for discussion prior to the surgery whenever possible. Subjects who undergo joint replacement or arthroplasty will be discontinued from study treatment and followed in a substudy as described in Appendix 16.

All female subjects who are of childbearing potential and are sexually active and at risk of pregnancy must agree to use one (1) highly effective method of contraception consistently and correctly for the duration of the active treatment period and for 112 days (16 weeks) after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected the most appropriate method of contraception for the individual subject from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for correct use of oneof the selected methods of contraception. The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the Schedule of Activities (SOA) and document such conversation in the subject's chart. In addition, the investigator or his or her designee will instruct the subject to call immediately if the selected contraception methods are discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following;[49]

1. Established use of hormonal methods of contraception is allowed provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness. Acceptable methods include:

    - combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

        - oral
        - intravaginal
        - transdermal

    - progestogen-only hormonal contraception associated with inhibition of ovulation[‡]:

        - oral
        - injectable
        - implantable

[‡] Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action is not accepted as a highly effective method.

2. Correctly placed intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).

3. Bilateral tubal occlusion.

4. Vasectomised partner provided that the partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success.

5. Sexual abstinence, defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

   NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

### 4.5. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the trial is documented in the study contact list located in the study manual.

To facilitate access to appropriately qualified medical personnel on study related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, subject study number, contact information for the investigational site and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subjects participation in the study. The contact center number can also be used by investigational staff if they are seeking advice on medical questions or problems, however it should be only used in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace the established communication pathways between the investigational site and study team for advice on medical questions or problems that may arise during the study. The contact center number is not intended for use by the subject directly and if a subject calls that number he or she will be directed back to the investigational site.

## 5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

## 5.1. Allocation to Treatment

Following implementation of protocol Amendment 3, subjects will be randomized at Baseline to one of the following treatments:

| Treatment Group |
|---|
| 1. Matching placebo for tanezumab SC once every 8 weeks x 3 administrations |
| 2. Tanezumab 20 mg SC once every 8 weeks x 3 administrations |

Subjects will be randomly assigned in a 1:1 ratio to the above treatment regimens according to a computer generated randomization code. Randomization will be stratified by (i) tumor aggressiveness (assessed by Eastern Cooperative Group [ECOG] performance status and (ii) presence/absence of concomitant anticancer treatment (eg, chemotherapy or hormonal therapy or anti-hormonal therapy). Randomization will be coordinated centrally through Interactive Response Technology (IRT). The system will provide subject identification numbers at Screening, which are subsequently linked to the treatment assignments at Randomization. A copy of the randomization code will be maintained by the sponsor by a person(s) who is independent of the trial conduct. It is the responsibility of the Principal Investigator to ensure that the subject is eligible for participation in the study before requesting Randomization. The study site will obtain the subject's randomization number and treatment assignment from the IRT. Further details are provided in the Pharmacy Manual.

Subjects randomized to the 10 mg dose treatment arm who are in the double-blind treatment period at the time of implementation of Amendment 3 will be administered 20 mg for any remaining doses. This will be managed through the IRT drug dispensing system in such a way as to not unblind anyone currently blinded during the study (eg, site staff, subject, sponsor study staff).

**Table 3. Stratification Randomization Scheme**

| Randomization Strata | Tumor Aggressiveness* | Concomitant anticancer treatment** |
|---|---|---|
| 1 | More aggressive | Present |
| 2 | More aggressive | Absent |
| 3 | Less aggressive | Present |
| 4 | Less aggressive | Absent |

* Screening ECOG performance status score of 0 or 1 corresponds to "less aggressive" tumor; Screening ECOG performance status score ≥2 corresponds to "more aggressive" tumor;

**Concomitant anticancer treatment as described in Section 5.8.2.

## 5.2. Breaking the Blind

This is a randomized, double-blind, parallel group study. The subjects, investigators, other clinical site staff, Clinical Research Associate (CRA), and staff directly involved with the study at Pfizer and its designees will be blinded to subject assignment.

At the initiation of the study, the study site will be instructed on the method for breaking the blind. The method will be either a manual or an electronic process. Blinding codes should

only be broken in emergency situations for reasons of subject safety. Whenever possible, the investigator or sub-investigator consults with a member of the study team prior to breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the case report form (CRF).

### 5.3. Subject Compliance

All doses of SC investigational product will be administered by the appropriately designated study staff at the investigational site. Tanezumab SC or matching placebo SC dosing will be recorded on the appropriate CRF. Because tanezumab or matching placebo will be administered by site staff, subject compliance with SC treatment is not anticipated to be an issue.

Compliance with background opioid therapy from Day 1 to Week 8 will be calculated within the IRT for one regimen. If more than one concomitant opioid is used, manual calculation by the sponsor will be undertaken to determine background opioid therapy dose.

### 5.4. Investigational Product Supplies

#### 5.4.1. Dosage Form(s) and Packaging

Tanezumab and matching placebo for tanezumab will be supplied by the sponsor or designee.

Tanezumab drug product and matching placebo for SC administration will be supplied in a single-use pre-filled syringe (PFS) that should be stored refrigerated at 2-8°C.

##### 5.4.1.1. Tanezumab

Tanezumab 20 mg is presented as a sterile solution for subcutaneous administration, packaged in a glass PFS. Each PFS contains a sufficient amount of tanezumab to provide the intended dose of drug at a concentration of 20 mg/mL. Each PFS is packaged in an individual carton. Each PFS has a unique container number.

Tanezumab 10 mg is presented as a sterile solution for subcutaneous administration, packaged in a glass PFS. Each PFS contains a sufficient amount of tanezumab to provide the intended dose of drug at a concentration of 10 mg/mL. Each PFS is packaged in an individual carton. Each PFS has a unique container number.

##### 5.4.1.2. Placebo for Tanezumab

Placebo for tanezumab is presented as a sterile solution for subcutaneous administration, packaged in a matching glass PFS. Each PFS is packaged in an individual carton. Each PFS has a unique container number.

Only tanezumab 20 mg and matching placebo for tanezumab will be supplied following implementation of protocol Amendment 3. Subjects randomized to the 10 mg dose treatment arm and who are in the double-blind treatment period at the time of implementation of Amendment 3 will be administered 20 mg for any remaining doses. Subjects who are randomized following implementation of protocol Amendment 3 will receive either tanezumab 20 mg or matching placebo.

### 5.4.2. Preparation and Dispensing

See the Drug Administration Instructions (DAI) for instructions on how to prepare tanezumab SC and matching placebo SC for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

## 5.5. Administration

Tanezumab or matching placebo will be administered via SC injection by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance and in facilities which can handle allergic reactions. All subjects will receive 1 mL of study medication administered as a SC injection. Subcutaneous injections are to be administered in the abdomen or anterior aspect of the thigh. Selection of the SC injection site for each injection will be at the discretion of the investigator taking into account subject preferences when possible. The SC injection should not be administered in areas where the skin is burned, reddened, inflamed, swollen, or scarred.

o Subcutaneous injection administered via any route other than subcutaneous (i.e. intramuscular, intravenous), is a medication error.

o Syringe (medical device) malfunction is a medication error (e.g.syringe/plunger breaks during administration).

Refer to section 8.4 Medication Errors for additional information.

Full dosage and administration instructions will be provided in the Pharmacist Manual. All local/state/federal laws must be complied with in assigning administration duties.

## 5.6. Investigational Product Storage

The Pharmacy Manual will provide complete details on storage and handling.

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the label. See the Pharmacy Manual for storage conditions of the product. Tanezumab and matching placebo will be shipped and stored at a temperature between 2° and 8°C and protected from light.

Storage conditions stated in the single reference safety document (ie, the Investigator Brochure) may be superseded by the storage conditions stated in the labeling.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as

applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout study. Even for continuous monitoring systems, a log or site procedure which ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to labeled storage conditions, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation.

The dispensing or administration of expired, quarantined, or improperly stored medication without prior approval from Pfizer Pharmaceutical Sciences (e.g. investigational product storage temperature excursion where subject was dosed with unacceptable drug per Pharmaceutical Sciences) is a medication error.

Refer to section 8.4 Medication Errors for additional information.

Specific details regarding information the site should report for each excursion will be provided to the site.

### 5.7. Investigational Product Accountability

The investigator or designated personnel must maintain adequate records documenting the receipt, use, loss, or other disposition of the drug supplies.

#### 5.7.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If Pfizer authorizes destruction to take place at the trial site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer. Destruction must be adequately documented.

### 5.8. Concomitant Treatment(s)

#### 5.8.1. Concomitant Treatment Prohibited During the Study

##### 5.8.1.1. Prohibited Background Opioid Treatment

The following opioids are not permitted in this study:

| | |
|---|---|
| butorphanol* | meperidine* |
| nalbuphine* | pentazocine* |
| propoxyphene ** | |
| opioids in combination with non-opioids (such as acetaminophen or NSAIDs)*** | |

* Use not recommended by NCCN Guidelines[27];
** Withdrawn from some major markets due to safety concerns
*** Opioids in combination with acetaminophen may be permitted as standard of care analgesia from Week 8 onwards. Opioid-NSAID combinations are prohibited throughout the study until at least 16 weeks have passed since the last dose of study medication (Week 32 or Early Termination Visit 2).

Permitted background opioid regimens are described in Section 5.8.2.1.

#### 5.8.1.2. Prohibited Non-opioid Analgesics

The use of analgesics (other than background opioids and permitted uses described in Sections 5.8.2) is prohibited throughout the study beginning 48 hours (or 5 half-lives, whichever is longer) prior to the start of the Baseline Assessment Period and ending at Week 8.

Use of NSAIDs and COX-2 selective inhibitors, both prescription or over-the-counter (OTC) is prohibited through Week 32 except for occasional use. Management of subjects' NSAID use is described below (Section 5.8.1.2.1). Intra-articular injection of corticosteroids to any major joint within 30 days prior to the Baseline Assessment Period through Week 32 is prohibited.

Unless the following drugs were started at least 30 days prior to the first day of the Baseline Assessment Period and are maintained at a stable dose, use of concurrent adjuvant analgesics such as single-agent acetaminophen (paracetamol), serotonin norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants, anticonvulsant medication, corticosteroids, or muscle relaxants is prohibited through Week 8.

Refer to Appendix 7: Half-Lives of NSAIDs and Other Analgesics, for a detailed washout schedule for analgesic medications. Sites must consult product labeling and conduct a taper according to the product instructions if a taper is required.

##### 5.8.1.2.1. Guidelines for Management of Subjects Reporting NSAID Use

Limited concomitant use of prescription or OTC NSAIDs may be allowed on an occasional basis for self-limiting conditions not related to cancer pain. However, they must not be taken within 48 hours of a study visit where efficacy assessments are being collected. Study management should be contacted for approval prior to use whenever possible, and all doses and days of use must be recorded on the concomitant analgesic CRF.

NSAID use should not exceed a total of 36 days between Day 1 (Baseline) and Week 32 and the aggregate usage of NSAIDs during any one dosing interval (defined as the period of 8 weeks between 2 SC doses) should not exceed 10 days.

Subjects who report concomitant use of prescription or OTC NSAIDs during the study prior to Week 32 will be managed as per the following guidelines:

- Subjects who report concomitant use of NSAID should be interviewed by study site personnel to determine the reason for use and if the subject anticipates being able to comply with concomitant medication restrictions in the future. Subjects who indicate they are taking NSAIDs because of insufficient cancer pain relief or who indicate that they cannot or will not be able to comply with concomitant medication restrictions will be withdrawn from study treatment and entered in the Early Termination Follow-Up period (refer to Section 6.4).

- Subjects who reported greater than 10 days (aggregate total) of concomitant NSAID use (any dosage of NSAIDs) in a SC dosing interval and who after counseling report further concomitant NSAID use should be withdrawn from study treatment and entered in the Early Termination Follow-Up period (refer to Section 6.4).

After Week 32, there are no restrictions on NSAID use provided the NSAID dosing is prescribed according to its approved label.

Subjects will be instructed that many over-the-counter medications contain NSAIDs and to be aware of this during their selection of OTC medications. Subjects who report concomitant NSAID use will be requested to provide details of the usage (dosage and reasons for use) which will be recorded in the appropriate concomitant medication case report form (CRF).

#### 5.8.1.3. Restrictions on Use of Treatments for Underlying Cancer or Bone Metastasis

Monoclonal antibodies used for the treatment of underlying cancer (eg, bevacizumab (Avastin), trastuzumab (Herceptin), panitumumab (Vectibix)) or bone metastasis (eg, denosumab (Prolia, Xgeva)) are generally permitted if ongoing at stable dose regimen at least 30 days prior to the first day of the Baseline Assessment Period (see Section 5.8.2.3). However, monoclonal antibody therapies associated with clinically significant peripheral or autonomic neuropathy or joint-related adverse effects or those based on chimeric or murine antibodies (eg, cetuximab (Erbitux)) are prohibited within 90 days of the start of the Baseline Assessment Period and during the study until Week 32. Monoclonal antibody therapies which are not specifically listed as permitted (see Appendix 8) should be discussed with the study clinician on a case-by-case basis.

Small molecule inhibitors (eg, erlotinib (Tarceva), sunitinib (Sutent), lapatinib (Tykerb)) used in the treatment of underlying cancer or bone metastasis are permitted (except for bortezomib) if at a stable dose regimen at least 30 days prior to the first day of the Baseline Assessment Period.

If during the double-blind treatment period prior to Week 8, the subject's underlying cancer or bone metastasis progresses so as to require a new chemotherapy regimen, new concomitant bisphosphonates, new concomitant hormonal anti-cancer treatment, or initiation of radiotherapy to sites of bone metastasis, the subject should be withdrawn from study treatment (eg, due to disease progression) and entered in the Early Termination Follow-Up period (refer to Section 6.4). Between Week 8 to Week 32, if treatment for underlying cancer

or bone metastasis needs to be initiated or changed (refer to Section 5.8.2.3), the study clinician should be informed so that guidance may be provided as to whether the subject should be withdrawn from study treatment and entered in the Early Termination Follow-Up period. After the Week 32 visit, standard of care treatment may be prescribed as appropriate, without prior consultation with the study clinician.

#### 5.8.1.4. Other Prohibited Medications

Herbal, homeopathic, and naturopathic remedies should not be initiated during the study; however, subjects who have taken a stable dose of these products for at least 30 days prior to start of the Baseline Assessment Period will be allowed to continue their regimen.

Cell/gene therapies, investigational therapies, or tumor necrosis factor alpha (TNF-α) inhibitors (eg, adalimumab, etanercept, infliximab) are generally prohibited and must not be taken within 90 days prior to start of the Baseline Assessment Period or during the study until Week 32. For further guidance, refer to Appendix 8 or contact study monitor or study clinician.

Live attenuated vaccines must not have been taken within 90 days prior to the Baseline Assessment Period and are prohibited during the study. Flumist® Influenza Virus Vaccine Live, Intranasal or other inhaled influenza vaccines (in regions where these vaccines are approved) is the only exception of a live attenuated vaccine that will be permitted during the study.

### 5.8.2. Permitted During the Study

#### 5.8.2.1. Background Opioid Treatment

The following oral or transdermal background opioid medications are permitted throughout the study:

| | | |
|---|---|---|
| buprenorphine | levorphanol | tapentadol |
| codeine | methadone | tramadol |
| fentanyl | morphine | |
| hydrocodone | oxycodone | |
| hydromorphone | oxymorphone | |

Tamper-resistant or opioid abuse-deterrent formulations (which may contain both an opioid agonist and an opioid antagonist) such as the following are permitted, for example:

- Embeda [morphine ER + naltrexone].
- Opana ER [oxymorphone ER with a crush-resistant matrix].
- Remoxy [oxycodone ER in highly viscous liquid gelatin capsule]).

Targin (ie, oxycodone/naloxone for opioid induced constipation) is also permitted.

Background opioids should consist of a fixed regimen of around-the-clock (ATC) opioid(s) plus supplemental "as needed" (rescue) doses of an immediate-release (IR) opioid as determined by the investigator and subject according to accepted clinical guidelines for opioid use. Refer to Section 6 for procedures regarding background opioids during the study.

#### 5.8.2.2. Permitted Non-opioid Analgesics

Concurrent adjuvant analgesics such as SNRIs, tricyclic antidepressants, anticonvulsant medication, single-agent acetaminophen (paracetamol) ≤3 grams/day for 3 days or less per week, corticosteroids, or muscle relaxants are allowed provided these drugs were started at least 30 days prior to start of the Baseline Assessment Period and are maintained at a stable dose through Week 8. With the exception of NSAIDs and intra-articular corticosteroids, standard of care analgesia is permitted starting at Week 8 (refer to Section 5.8.2.5 and 6.3). Use of NSAIDs or intra-articular corticosteroids as part of standard of care analgesia is permitted beginning 16 weeks after the last dose of subcutaneous study medication.

Occasional use of acetaminophen (paracetamol) (eg, ≤3 grams/day for 3 days or less per week) for pain conditions other than cancer pain is permitted.

In certain circumstances, occasional use of usually-prohibited analgesics (eg, NSAIDs) may be permitted. Such circumstances could include outpatient diagnostic procedures (eg, colonoscopy, dental procedures) or limited accidental injury (eg, ankle sprains, minor fractures, minor burns/sunburns). Refer to Section 5.8.1 for limitations and prohibitions on these analgesics. Subjects should also be counseled to avoid scheduling prospective procedures such that pain medications would be needed within 48 hours of a study visit. Limited use of oral, intramuscular or intravenous corticosteroids for non-analgesic purposes such as prophylaxis or treatment of chemotherapy-induced nausea and vomiting is permitted. However, they must not be taken within 48 hours of a study visit where efficacy assessments are being collected. Topical, inhaled and intranasal corticosteroids are permitted. Contact the assigned study monitor or study clinician for guidance/approval regarding the use of prohibited medications for other self-limiting conditions, accidental injury or other surgical procedures as the extent of the condition, injury or procedure and the resulting pain medication usage may require termination from the study.

#### 5.8.2.3. Permitted Concomitant Treatments for Underlying Cancer or Bone Metastasis

Concomitant anticancer treatment of the subject's underlying primary cancer or bone metastasis is permitted as follows:

- Concomitant chemotherapy, other than paclitaxel, docetaxel, oxaliplatin, cisplatin, vincristine, thalidomide and bortezomib or those expressly prohibited (see Appendix 8), is allowable provided it was ongoing for at least 30 days before the first day of the Baseline Assessment Period. It is acceptable for the regimen to complete at any time after Randomization.

    - Paclitaxel, docetaxel, oxaliplatin, cisplatin, vincristine, thalidomide and bortezomib are not permitted from 30 days prior to the first day of the Baseline Assessment Period to Week 48.

    - A subject with chemotherapy-induced peripheral neuropathy can be enrolled provided the neuropathy has been stable over the 6 months prior to the start of the Baseline Assessment Period and the subject is no longer being treated with a chemotherapy agent associated with peripheral neuropathy.

- Monoclonal antibody therapies used in the treatment of underlying cancer or bone metastasis are allowed (with some exceptions; refer to Section 5.8.1.3 ) if part of a stable dose regimen started at least 30 days prior to the first day of the Baseline Assessment Period. It is acceptable for the regimen to complete at any time after Randomization; however, if new treatment is initiated prior to Week 8, the subject should be withdrawn from study treatment. Refer to Appendix 8.

    - Monoclonal antibody therapies associated with clinically significant peripheral or autonomic neuropathy or joint-related adverse effects or those based on chimeric or murine antibodies (eg, cetuximab (Erbitux)) are prohibited within 90 days of the start of the Baseline Assessment Period and during the study until Week 32. Refer to Section 5.8.1.3.

- Small molecule inhibitors used in the treatment of underlying cancer or bone metastasis (eg, erlotinib (Tarceva), sunitinib (Sutent)) are permitted (except for bortezomib) during the study if initiated at least 30 days prior to the first day of the Baseline Assessment Period and maintained at stable dose during the double-blind treatment period to at least Week 8.

- Blood and blood products for transfusion are allowed throughout the study.

- Concomitant hormonal anti-cancer treatment (eg, GnRH agonists or antagonists, anti-androgens or anti-estrogens) is allowable if treatment has been ongoing at stable dose for at least 30 days prior to the first day of the Baseline Assessment Period and bone pain still is severe enough to meet inclusion criteria. Post-Baseline, the concomitant hormonal anti-cancer treatment dose regimen should remain stable through at least Week 8.

#### 5.8.2.4. Other Permitted Medications

Medications for other (non-cancer, non-pain) conditions are permitted. Dose adjustments (includes starting a new therapy) during the study can be made if required, and recorded on the concomitant medication CRF.

Daily low dose aspirin (≤325 mg as per local prescribing practice) therapy for cardiovascular prophylaxis is permitted without restriction.

#### 5.8.2.5. Standard of Care Analgesia (after Week 8)

With the exception of NSAIDs or intra-articular corticosteroids, beginning at Week 8 (or Early Termination Visit 1), the investigator may prescribe standard of care analgesia for subjects intending to complete the 24-week Safety Follow-Up period. In this study, standard of care analgesia refers to treatments approved by FDA (for US subjects) or another

applicable Health Authority (for non-US subjects) to relieve the cancer pain. These medications may include opioids, topical analgesics, capsaicin products and are prescribed at the discretion of the investigator.

Standard of care analgesia may include NSAIDs or intra-articular corticosteroids, but these agents should not be re-instituted on a regular basis until at least 16 weeks have passed since the last dose of study medication (Week 32 or Early Termination Visit 2), in order to ensure tanezumab has been eliminated and to minimize joint safety risk. Standard of care analgesics are not considered study medication but will be reimbursed by Pfizer from Randomization, if allowed per local regulation, while the subject is participating in the study. Cancer or bone metastasis therapies are not reimbursed by Pfizer.

#### 5.8.2.6. Standard of Care Treatment for Underlying Cancer or Bone Metastasis (after Week 8)

Between Week 8 to Week 32, if treatment for underlying cancer or bone metastasis needs to be initiated or changed (refer to Section 5.8.2.3), the study clinician should be informed so that guidance may be provided as to whether the subject should be withdrawn from study treatment and entered in the Early Termination Follow-Up period. Following Week 32, cancer or bone metastasis treatment may be instituted in accordance with standard of care without prior consultation of the study clinician.

## 6. STUDY PROCEDURES

Refer to Schedule of Activities Table 1 and Table 2 for the lists of procedures to be performed throughout the study.

As a general rule, scales/instruments should be completed first by the subject upon arrival at the clinic and vital signs should be assessed prior to blood draws. If possible, each subject's clinic visits should be conducted at approximately the same time of day.

Subjects should be thoroughly instructed on completion of the scales/instruments via IRT prior to completing them the first time (at Screening for PGA of Cancer Pain CCI at Baseline for CCI OR-SDS CCI questionnaires). No coaching or other interpretative assistance should be given to subjects during completion of these questionnaires.

The windows for study visits (in clinic and phone contacts) are ±3 days for the Week 2 to Week 16 visits, ±5 days for the Week 20 to Week 28 visits, and ±7 days for the Week 32 to Week 48 visits. Study visits should be scheduled with reference to the study drug dosing date as much as possible. Subject scheduling issues should be brought to the attention of the study monitor for resolution. Dosing visits should occur no earlier than 7 weeks from the previous injection. The visit window for the Week 24 x-rays is ±30 days from the nominal time point of the visit. The Week 48 x-rays should be obtained within a ±30 day visit window, preferably prior to the Week 48 visit, but if possible, no more than 14 days after the Week 48 visit. In Japan only, the Week 16 x-rays may be obtained up to 7 – 21 days before the Week 16 visit (Week 14 ± 7 days).

## 6.1. Pre-Treatment Period

The Pre-Treatment Period of the study consists of a Screening Period lasting ≤32 days and a Baseline Assessment Period lasting 5 days. Subjects with a Pre-treatment Period lasting longer than 37 days eg, due to scheduling delays, should be discussed with the study team prior to Randomization. Subjects may be permitted to re-screen eg, due to resolution of exclusionary condition, with prior agreement of the study team.

Prior to entering the study, subjects must have been diagnosed with cancer and have moderate to severe pain due to bone metastasis despite treatment with an allowable regimen of opioids.

### 6.1.1. Screening Period

Although it is generally expected that most Screening activities will occur at the initial Screening visit, additional visits during the Pre-Treatment period may be required in order to perform protocol-required activities (eg, repeat laboratory testing, imaging scheduling, subject diary IRT set-up).

#### 6.1.1.1. Activities Performed at the Screening Visit

##### 6.1.1.1.1. Assessment of Inclusion and Exclusion Criteria

After obtaining informed consent at Screening, the investigator will obtain information and perform activities listed in the Schedule of Activities. Refer to Schedule of Activities Table 1 for an all-inclusive list of procedures to be performed at the Screening Visit and Section 7 for descriptions of the assessments.

Subjects requiring background regimens of a number of oral or transdermal opioids will be eligible. Refer to Section 5.8 for permitted and prohibited background opioid regimens.

If imaging (eg, bone scan) is not available within 120 days of the Screening visit for confirmation of the presence of bone metastasis, the subject will undergo appropriate imaging confirmation during the Screening Visit or Screening Period according to local standard of care. It is generally expected that confirmation will take place at the Screening Visit, prior to setting the subject up with an IRT subject diary, unless the imaging confirmation of bone metastasis (if required) cannot be performed at the Screening Visit or if further testing is needed. In this case, the subject diary IRT set-up will be finalized after confirmation has taken place.

##### 6.1.1.1.2. Subject Completion of Screening Assessments

IRT will be used by the subject to complete assessments as described in the Schedule of Activities Table 1 (eg, PGA of cancer pain, CCI assessments of pain at cancer sites and pain in major joints). Refer to Section 7 for details of these assessments.

Site staff will instruct the subject on completion of the initial IRT assessments and the subject will then complete these assessments independently.

#### 6.1.1.1.3. Selection of Index Bone Metastasis Site and Non-index Cancer Pain Sites

At the initial Screening Visit, the subject will record an initial average and worst daily pain score with an 11-point numerical rating scale (NRS) via IRT for the most painful site of bone metastasis (the index bone metastasis cancer pain site) and for up to 2 other (non-index) sites of cancer pain (which could be due to bone metastasis pain or other types of cancer pain). The investigator will confirm that the site identified by the subject as the most painful site corresponds to a site of bone metastasis.

If the investigator is unable to confirm this, but considers that such confirmation could be made based upon additional imaging information (eg, bone scan, MRI), then such additional imaging is permitted. In this case, subject diary IRT set-up should be deferred until after confirmation has taken place.

For the other non-index sites of cancer pain selected by the subject, the investigator will confirm that the pain at each site is due to cancer or cancer treatment (eg, chemotherapy induced peripheral neuropathy) and whether in his/her judgment the cancer pain for each site is primarily somatic, neuropathic or visceral in nature. Once the index and non-index sites are identified and confirmed, the IRT will indicate the location(s) the subject selected when the subject is subsequently asked to provide pain ratings.

Appendix 15 provides a scenario example of how a subject might select painful sites at Screening using a body diagram (with confirmation by the investigator).

### 6.1.1.2. Screening Activities Initiated at the End of the Initial Screening Visit in Subjects Meeting Criteria up to That Point

#### 6.1.1.2.1. Washout of Prohibited Pain Medications

The Screening Period will include the discontinuation and washout of all prohibited pain medications (eg, NSAIDs) for at least 5 times the elimination half-life prior to the Baseline Assessment Period.

#### 6.1.1.2.2. Schedule Screening X-rays of Major Joints

At the initial Screening Visit, the subject will have provided an average pain score (scored with an 11-point NRS via IRT) for the shoulders, hips and knees and any other joint for which a radiograph is to be obtained. The investigator will indicate whether or not pain reported in the major joints noted above is considered related to cancer or cancer treatment.

The subject will then be scheduled for x-rays of each of the subject's knees, hips, and shoulders. All x-rays will be evaluated by a Central Reader to determine the subject's radiographic eligibility for the study. Other major joints exhibiting signs or symptoms suggestive of osteoarthritis should also be imaged. The average pain score, recorded by the subject at the Screening visit via IRT, for the shoulders, hips and knees (and any other joint for which a radiograph is obtained) will be reviewed by the Central Reader with the x-rays. Refer to Section 7.3.9 for details regarding x-ray evaluation. Subjects with clinical and radiographic evidence of osteoarthritis of the knee, hip or shoulder or other pre-specified joint abnormalities (as described in Exclusion Criteria) will be excluded from study participation.

#### 6.1.1.2.3. Instruct Subject on Completion of Daily/Weekly IRT Assessments (Subject Diary)

Site staff will instruct the subject on completion of daily/weekly IRT assessments. During the Pre-Treatment Period, the subject will use the IRT to record average and worst daily pain scores each day for the index bone metastasis cancer pain site and each week for non-index cancer pain sites, based on a 24-hour recall period. (Refer to Section 7.1.1 for details regarding pain assessments.) Each day during the Pre-Treatment Period the subject will also record via IRT the amount of opioid taken and whether s/he is having intolerable opioid side effects.

#### 6.1.1.2.4. Adjustment of Background Opioid Regimen

During the Pre-Treatment Period, the total daily dose of a fixed regimen of ATC opioid(s) plus supplemental "as needed" (rescue) doses of IR opioid will be determined by the investigator and subject according to accepted clinical guidelines for opioid initiation and adjustment, such as the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Adult Cancer Pain.[46] The purpose is to determine the optimal total daily dose of opioid medication using a stable ATC regimen of opioids and IR opioids as needed for breakthrough pain. Each day the subject will record via IRT (subject diary) the amount of ATC and IR opioids taken, the number of times rescue medication was taken, and whether or not opioid pain medication side effects are tolerable.

Based on subject responses recorded in the IRT, study site personnel will contact (eg, by telephone call) the subject as needed for the purposes of determining and prescribing an optimal regimen of background opioids. Opioid dose recommendations will be made based on accepted clinical guidelines.

Doses may be changed at each assessment during the Pre-Treatment Period (no more often than daily). Doses need not be changed if the investigator chooses to observe the subject longer at a given dose, if side effects are tolerable, or if the ATC regimen is considered to be stable and tolerable and the subject is able to enter the Baseline Assessment Period. Investigators and subjects should be aware that subjects on a stable opioid regimen who meet the criteria for randomization during the Baseline Assessment Period will need to continue on the opioid regimen with minimal dosage increases permitted for the first 8 weeks of the Double-Blind Treatment Period.

**Note**: In the event that Screening activities cannot be completed within 32 days of signing informed consent (eg, due to unavoidable delays in scheduling), investigators should contact the study team to confirm whether the subject may continue in the study and if additional steps are required (eg, re-consent of subject, repeat of study procedures).

### 6.1.2. Baseline Assessment Period (BAP, Days -5 to -1)

The purpose of the Baseline Assessment Period is to determine the Baseline pain value for each subject and to document that the subject's background opioid regimen is sufficiently robust to minimize the need for opioid IR rescue but also tolerable as judged by the subject. These data will confirm that Randomization Criteria 1, 2 and 3 have been met. Refer to Section 4.3 for Randomization Criteria details.

Subjects who remain eligible and who are tolerating a stable ATC regimen of opioids can begin the Baseline Assessment Period approximately 5 days prior to the Baseline (Day 1) randomization visit.

During the Baseline Assessment Period, the subject will record daily pain scores for his/her cancer pain sites and opioid medication use via the IRT (refer to Section 7.1.1). The daily average pain score in the index bone metastasis site and daily opioid use collected via IRT should be reviewed by study site staff to assess compliance with the subject diary and need for dose adjustments. Each day the subject will record via IRT (subject diary) the amount of ATC and IR opioid taken, the number of times rescue medication was taken, and whether or not opioid pain medication side effects are tolerable.

**Note:** In the event a subject misses an assessment day in this Baseline Assessment Period, the schedule may be adjusted to acquire the 5 days of assessment entry into the IRT. Study sites will monitor the IRT reports for compliance with diary recordings and rescue medication use and reschedule those subjects who fail to provide at least the final 3 days of diary data (Day -3 to Day -1).

## 6.2. Double-Blind Treatment Period

The day after the 5-day Baseline Assessment Period is complete, eligible subjects will be randomized and enter the 24-week Double-Blind Treatment Period.

The Double-blind Treatment period begins with the Baseline (Day 1) visit and concludes with completion of the Week 24 visit procedures. The Double-blind Treatment period is 24 weeks in duration and consists of 6 clinic visits (Day 1 and Weeks 2, 4, 8, 16, and 24) and 2 telephone contacts (Weeks 12 and 20) between site staff and study subjects. Week 8 and Week 16 are dosing visits.

### 6.2.1. Randomization Clinic Visit

#### 6.2.1.1. Pre-Randomization

Full eligibility prior to randomization includes (but is not limited to) radiographic confirmation of bone metastasis, confirmation of Randomization Criteria (including those regarding Baseline PGA criteria and confirmation of Central Reader eligibility for each hip, knee and shoulder x-ray), confirmation of appropriate washout of concomitant medications and confirmation that no adverse events occurred since signing informed consent that would render the subject ineligible for randomization.

Refer to the Schedule of Activities Table 1 for the activities which should be completed prior to randomization to confirm eligibility for randomization.

#### 6.2.1.2. Randomization

Subjects must satisfy all Inclusion, Exclusion and Randomization Criteria to be eligible for randomization. Refer to Sections 4.1, 4.2, and 4.3, respectively.

Following confirmation of eligibility, subjects will be randomized via an IRT system, which will assign a randomization number to the subject

#### 6.2.1.3. Dosing (Day 1)

After randomization, subjects will receive a single SC injection of blinded study medication according to the treatment assigned by the IRT system (refer to Section 5.1).

The administration of study drug must be performed by trained medical staff and where facilities to handle allergic reactions are available. Should a subject experience symptoms typical of an allergic reaction, then study drug administration should be discontinued immediately and permanently. No other dosage modifications are allowed.

#### 6.2.1.4. Post-dosing

Subjects will be observed for adverse events including signs and symptoms of hypersensitivity or injection reactions in the clinic for a minimum of 1 hour after administration of SC study medication.

The following procedures will be completed at approximately 1-hour post-dose:

- Review and record adverse events.
- Each subject should be reminded to seek medical care and/or contact the investigator if the subject experiences symptoms of an acute or severe hypersensitivity reaction after leaving the clinic.
- If not done before, female subjects of child bearing potential will be reminded of contraceptive requirements.

### 6.2.2. Double Blind Treatment Period

#### 6.2.2.1. Background Opioid Use

After randomization and through Week 8, all subjects will continue to take the opioid regimen or morphine equivalent dose used during the Baseline Assessment Period. The average of the total daily opioid doses (ATC + IR) taken during the Baseline Assessment Period will be used as the Baseline total daily opioid dose.

Beginning on Day 1 and through Week 8, the average total daily dose of opioids between study clinic visits should not exceed the Baseline total daily morphine equivalent opioid dose by more than 10%. Subjects who require an opioid dose more than 10% greater than the Baseline total daily opioid dose should discontinue the Double-Blind Treatment Period for insufficient clinical response or disease progression ( per investigator's judgment) and enter the 6-month Safety Follow-Up period (refer to Section 6.4). Opioid dose reduction will be allowed if the subject experiences intolerable opioid side effects, if pain decreases or if the subject requests dose reduction. Once reduced, the opioid dose may be re-increased if needed for pain relief, but should not exceed the Baseline total daily morphine equivalent opioid dose by more than 10%.

Following the Week 8 clinic visit, subjects will remain on the opioid regimen used during the Baseline Assessment Period but will be allowed to change formulation, increase or decrease the amount of their background opioid medication without restriction if the investigator

considers such changes are necessary. Opioid reductions and increases will be done using accepted clinical guidelines (refer to Section 6.1.1.2.4).

#### 6.2.2.2. Concomitant Treatment for Underlying Cancer or Bone Metastasis

Beginning at Week 8, additional changes to underlying cancer or bone metastasis therapy or pain treatment regimen may be initiated by the investigator to provide standard of care treatment (with the exception of NSAIDs) if determined appropriate (refer to Section 5.8.2.6). If treatment is initiated or changed between Week 8 to Week 32, the study clinician should be informed so that guidance may be provided as to whether the subject should be withdrawn from study treatment and entered in the Early Termination Follow-Up period.

#### 6.2.2.3. IRT (Subject Diary)

Beginning with the Pre-Treatment Period and through Week 8, the subject will record via IRT (subject diary) average and worst daily pain scores each day for the index bone metastasis cancer pain site, the amount of background opioid taken each day, and will record average and worst daily pain scores each week using a 24-hour recall period for non-index cancer pain site(s).

After Week 8 and through Week 24, each of these assessments will be collected weekly using a 24-hour recall (see Section 7.1.1).

Beginning with the Pre-Treatment Period and through Week 48, each week the subject will be asked via IRT if he or she experienced new onset or increased pain in a major joint (refer to Section 7.1.1.3). If the subject reports new onset or increased pain in a major joint (Post-Baseline), the subject will be asked to rate his/her pain in that joint on an 11-point NRS, using a 24-hour recall period and to rate his/her pain in that joint for the remainder of the study. Subjects with severe, persistent joint pain will have more detailed evaluations to investigate this (refer to Section 7.4.4).

On a weekly basis from Baseline (Day 1) and through Week 48, the subject will also be asked via IRT to record the number of days of NSAID use in the past week. Details of the NSAID use will be collected by the site (eg, via phone contact) as described in Section 7.1.3.

#### 6.2.2.4. Routine Clinic Visits (Week 2 and Week 4)

The subject will return for clinic visits at Week 2 and Week 4 to be assessed for efficacy and safety. Refer to Schedule of Activities Table 1 for the procedures to be performed at the Week 2 and Week 4 Visits.

#### 6.2.2.5. Dosing Visits (Week 8 and Week 16)

- The subject will return for clinic visits at Week 8 and at Week 16 to be assessed for efficacy and safety. At Week 8 and Week 16 the subject will receive the second and third administrations of SC study medication, respectively. Refer to Schedule of Activities Table 1 for the procedures to be performed at the Week 8 and Week 16 Clinic Visits. The dosing and post-dosing procedures are the same as those as described in Sections 6.2.1.3 and 6.2.1.4.

**NOTE**: In Japan only, confirmation of continued radiographic eligibility from the Central Reader is required before Week 16 dosing. The X-rays (knees, hips and shoulders, and any other major joint imaged at Screening or at-risk joint identified during the study period) may be obtained up to 7 – 21 days before the Week 16 visit (Week 14 ± 7 days) in order to allow confirmation of continued radiographic eligibility from the Central Reader.

#### 6.2.2.6. Phone Contact Visits (Week 12 and Week 20)

The subject will be contacted by telephone at Week 12 and at Week 20 to review adverse events, concomitant medications, compliance with daily/weekly IRT entries and to remind female subjects of contraceptive requirements.

Refer to Schedule of Activities Table 1 for the procedures to be performed at the Week 12 and Week 20 Phone Contacts.

- At the Week 20 phone call, schedule Week 24 x-rays, to occur preferably prior to the Week 24 visit but if possible, no more than 30 days after the Week 24 clinic visit.

#### 6.2.2.7. Week 24 Clinic Visit (End of Double-Blind Treatment)

The subject will return for a clinic visit at Week 24 to be assessed for efficacy and safety. Refer to Schedule of Activities Table 1 for the procedures to be performed at Week 24 Clinic Visit and Section 7 for more details on these procedures.

- With the completion of the Week 24 visit, the subject will begin the 24-week Safety Follow-Up Period. Given the design of this study, which includes a 24 week Safety Follow-Up period during which subjects no longer receive study medication and receive standard-of-care treatment from Week 8, additional investigational product at the conclusion of the study will not be provided.

- Only subjects who complete the Week 24 assessments will be considered to have completed the Double-Blind Treatment Period.

### 6.3. Safety Follow-Up Period

Subjects who enter the Safety Follow-Up period after completion of the Double-Blind Treatment period and the Week 24 visit will be followed for an additional period of 24 weeks. This will include 2 clinic visits (Weeks 32 and 48) and 4 telephone contacts (Weeks 28, 36, 40 and 44) between site staff and enrolled subjects. For Japan only, the Week 40 visit will be in-clinic.

During the Safety Follow-Up period (after the Week 24 visit), the subject will no longer report cancer pain scores in the IRT (subject diary) for purposes of efficacy assessments. The subject will only provide a weekly assessment of joint pain (shoulders, hips and knees) and any NSAID use via IRT using a 24-hour recall period through Week 48.

From Week 24 to Week 32, the subject will continue to use opioids for cancer pain treatment (which as noted in Schedule of Activities Table 1 (footnote l) may have been liberalized

beginning as early as Week 8). Any needed opioid dose adjustments during this period should continue to follow accepted clinical guidelines (as described in Section 6.1.1.2.4).

If needed, beginning at Week 32, treatment with NSAIDs may proceed without restriction, but within approved label instructions.

At Week 48, the subject will return for the final End-of-Study clinic visit. At this visit, all End-of-Study procedures are to be completed, including general physical CCI CCI x-rays of each knee, hip and shoulder, laboratory assessments and other safety assessments as described in the Schedule of Activities. X-rays of each shoulder, hip and knee as well as any additional joint that was imaged at Screening or identified as at risk during the study will be obtained. These images will be sent to the blinded Central Reader for review.

### 6.3.1. Week 32 Clinic Visit

The subject will return for a clinic visit at Week 32 to be assessed for safety. Refer to Schedule of Activities Table 1 for the procedures to be performed at the Week 32 Visit.

### 6.3.2. Phone Contacts (Weeks 28, 36, 40, and 44); for Japan only, Week 40 Clinic Visit

The subject will be contacted by telephone at Weeks 28, 36, 40 and 44 to review adverse events, concomitant medications, compliance with daily/weekly IRT entries and, at Week 28 phone call only, to remind female subjects of contraceptive requirements.

Refer to Schedule of Activities Table 1 for the procedures to be performed at the Weeks 28, 36, 40 and 44 Phone Contacts.

At the Week 44 phone call, schedule Week 48 x-rays, to occur preferably prior to the Week 48 visit but if possible, no more than 14 days after the Week 48 Clinic Visit.

**Note**: In Japan only, subjects will return for a clinic visit at Week 40 to review adverse events, concomitant medications, compliance with daily/weekly IRT entries. Refer to Schedule of Activities Table 1 for the procedures to be performed at the Week 40 clinic visit.

### 6.3.3. Week 48 Clinic Visit (End of Study)

The subject will return for the end of study clinic visit at Week 48 to be assessed for safety. Refer to Schedule of Activities Table 1 for the procedures to be performed at the Week 48 (End of Study) Clinic Visit.

## 6.4. Subject Withdrawal/Early Termination

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if

possible. The investigator should inquire about the reason for withdrawal, follow-up with the subject regarding any unresolved adverse events and request that the subject return for follow-up visits as indicated in the schedule below. Subjects of child-bearing potential should be reminded to continue contraceptive measures at least 112 days (16 weeks) after the last dose of study medication.

If the study medication and the allowable background opioid regimen are not providing acceptable pain relief during the double-blind treatment period, the subject should be withdrawn from study treatment (eg, due to lack of efficacy or disease progression per the investigator's judgment) and entered in the Early Termination Follow-Up period.

Subjects discontinuing from treatment (prior to Week 24), either at their request or at the decision of the investigator, will be asked to undergo 24 weeks of post-treatment follow-up (as described in Section 6.4.1). The 24 weeks of follow-up will be obtained through 3 clinic visits and monthly phone calls to yield 24 weeks of follow-up, as described in Section 6.4.1. In addition, subjects will be asked to continue to enter pain scores for index and non-index cancer pain sites and for major joints via IRT, weekly, until 16 weeks after the subject's last dose of SC study treatment (for cancer pain scores) and through the end of the 24 Week Safety Follow-Up period (for joint pain scores).

In the event a subject refuses the Early Termination Safety Follow-Up, or chooses to discontinue during the Safety Follow-Up (after Week 24 and through Week 48), a complete Early Termination visit should be performed that should include all procedures described in Section 6.4.1.1 Early Termination 1 (also described in Table 2 column 3), including the x-rays of major joints provided at least 30 days have elapsed since the last x-rays were collected (see Section 6.4.1 and Table 2 column 2). In addition, female subjects will be advised to continue their contraception regimen during a period of 112 days (16 weeks) after the last dose of SC study medication.

Withdrawal of Consent: Subjects who request to discontinue study treatment will remain in the study and will continue to be followed for protocol specified follow-up procedures unless they specifically withdraw consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page. If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. Pfizer may retain and continue to use any data collected before such withdrawal of consent.

Lost to Follow-Up: All reasonable efforts must be made to locate subjects as to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to Follow-Up is defined by the inability to reach the subject after a minimum of three documented contacts (via phone calls, faxes, and/or emails) as well as lack of response by subject to one registered mail letter. All attempts should be

documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death. If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains Lost to Follow-Up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

Brief summary of procedures for subjects discontinuing from study treatment

X-rays of the knee, shoulder and hip (and any other joint imaged at Screening or identified as at risk during the study) should be performed as soon as possible after the decision to withdraw from the study has been made, provided at least 30 days have passed since the last set of x-rays were collected (refer to Section 6.4.1).

The remainder of efficacy and safety assessments should be done at the scheduled first visit which is to occur approximately 8 weeks after the last dose of SC study treatment (refer to Section 6.4.1.1, Early Termination Visit 1). The site should also schedule the subject for two additional clinic visits. The second visit should be scheduled to occur approximately 16 weeks after the subject's last dose of SC study treatment (corresponding to more than 5 times the elimination half-life of tanezumab) to collect safety and efficacy data (refer to Section 6.4.1.3, Early Termination Visit 2). Once the clinic visit 16-weeks after the last administration of SC study treatment has been completed and final efficacy assessments have been collected, standard of care analgesia with NSAIDs or intra-articular corticosteroids may be offered to subjects who are completing the remaining 8 weeks of the required follow-up period. The third and final clinic visit should be scheduled to take place approximately 24-weeks after the subject received the last dose of SC study treatment (refer to Section 6.4.1.4, Early Termination Visit 3). Telephone contact will be made with subjects at approximately 12 and 20 weeks following the last SC dose of study treatment. Every effort should be made to have the subject agree to complete the entire 24-week Early Termination Safety Follow-Up described in Section 6.4.1.

Subjects entered in the Early Termination Follow-Up period will be able to take background opioid medication daily up to the Early Termination Follow-Up period Visit 3 (which occurs 24 weeks after the last dose of SC study treatment.

### 6.4.1. Early Termination Follow-Up Procedures

As soon as possible following a decision to withdraw a subject from the study is made, provided at least 30 days have passed since the last set of x-rays were collected, x-rays of all joints for which x-rays were obtained at Screening and other at risk joint identified during the study period should be obtained (refer to Section 7.3.9). X-rays should be submitted to imaging Central Reader.

Refer to the Early Termination Schedule of Activities Table 2.

#### 6.4.1.1. Early Termination Visit 1 (~8 Weeks after Last Dose of SC Study Medication)

Refer to the Early Termination Schedule of Activities Table 2 and Section 7 for information on the procedures to be performed at Early Termination Visit 1.

#### 6.4.1.2. Early Termination Telephone Contacts 1 and 2 (~12 Weeks and ~20 Weeks after Last Dose of SC Study Medication)

The subject will be contacted by telephone twice (~12 weeks and ~20 weeks after the last dose of SC study medication) to review adverse events, concomitant medications, compliance with daily/weekly IRT entries and, at Telephone contact 1, to remind female subjects of contraceptive requirements.

Refer to the Early Termination Schedule of Activities Table 2 for the procedures to be performed at the Early Termination Telephone Contacts.

At Telephone Contact 2, schedule x-rays, to occur preferably prior to the Early Termination Visit 3 but if possible, no more than 14 days after the Early Termination Visit 3.

#### 6.4.1.3. Early Termination Visit 2 (~16 Weeks after Last Dose of SC Study Medication)

Refer to the Early Termination Schedule of Activities Table 2 and Section 7 for information on the procedures to be performed at Early Termination Visit 2.

#### 6.4.1.4. Early Termination Visit 3 (~24 Weeks after Last Dose of SC Study Medication)

Refer to the Early Termination Schedule of Activities Table 2 and Section 7 for information on the procedures to be performed at Early Termination Visit 3.

### 6.5. Procedures for Subjects Undergoing Joint Replacement

Subjects who have undergone or plan to undergo total joint replacements or other arthroplasty procedure during the study will be discontinued from study treatment. Follow-up procedures for these subjects are described in Section 7.4.6. In addition, subjects who undergo total knee, hip or shoulder joint replacement surgery during the study (Double-Blind Treatment Period or Safety Follow-Up Period) will be followed for 24 weeks after the procedure as part of a separate substudy, described in Appendix 16, provided the subject consents.

## 7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

## 7.1. Subject IRT Assessments

The subject IRT assessments described in this section should be completed in the evenings if possible.

### 7.1.1. Daily/Weekly Pain IRT Assessments

Average pain and worst pain in the index bone metastasis cancer pain site, non-index cancer pain sites and average pain in painful major joints will be assessed by the subject at approximately the same time each day (or each week) with an 11-point Numeric Rating Scale (NRS) ranging from 0 (no pain) to 10 (worst possible pain) captured through IRT. The subjects should describe their pain in the painful site during the past 24 hours by choosing the appropriate number from 0 to 10.

Subjects will record diary entries in an electronic IRT tool. Although the subject is responsible for completing the diary, the site personnel have a number of responsibilities related to the IRT including:

- Assigning, setting up and collecting the IRT devices.
- Instructing subjects on IRT diary use and transmission of data.
- Reviewing subject's IRT (subject diary) during the Screening period (including Baseline Assessment Period) and at each study visit (including phone contact visits) to ensure completeness (eg, by using the IRT vendor's trial manager). Questioning subjects for missing entries and retrain as appropriate. If the issue is technical, work with the subject and/or the IRT vendor to address the problem.
- Reviewing daily and weekly (as applicable) IRT (subject diary) entries.

#### 7.1.1.1. Index Bone Metastasis Cancer Pain Site Assessment

At Screening, subjects will be asked to identify the most painful site of bone metastasis via IRT. This site will be considered the index bone metastasis cancer pain site. Subjects will be asked to record daily pain ratings for the index bone metastasis cancer pain site as described below.

Average pain and worst pain in the index bone metastasis cancer pain site will be assessed by the subject at Screening and daily during the Pre-Treatment Period to the Week 8 Visit, and then will be assessed weekly using a 24-hour recall period beginning after the Week 8 visit through Week 24 (and weekly during the Early Termination Follow-Up Period, as shown in Table 2). Refer to Appendix 9 to see examples of the questions the subject will be asked.

#### 7.1.1.2. Non-Index Site(s) of Cancer Pain Assessment

At Screening, subjects will be asked via the IRT whether they are experiencing cancer pain in site(s) other than the index bone metastasis cancer pain site. If so, they will be prompted to identify up to 2 other site(s), which will be considered a non-index cancer pain site(s). If the subject has more than 2 other painful cancer pain sites, he or she should select the 2 sites which are most painful as the non-index cancer pain sites. Subjects will rate their average

pain and worst pain for each site(s) with an 11-point Numeric Rating Scale ranging from 0 (no pain) to 10 (worst possible pain) during the past 24 hours.

Assessment of pain in non-index site(s) of cancer pain will be performed weekly during the Pre-Treatment Period to the Week 24 Visit (and weekly during the Early Termination Follow-Up Period up to the visit that occurs 16 weeks after the last dose of SC study medication was administered). Refer to Appendix 9 to see examples of the questions the subject will be asked.

#### 7.1.1.3. Joint Pain Assessments

Pain in each shoulder, hip and knee and any additional major joint that will be imaged at Screening (refer to Section 7.3.9), will be assessed via IRT at the Screening Visit using the 11-point NRS scale noted below. These joint pain assessments are conducted for joint safety purposes, not for efficacy assessments. Refer to Appendix 9 to see an example of the question the subject will be asked.

Thereafter, on a weekly basis beginning during the Pre-Treatment Period and through Week 48 (or Early Termination as described in Section 6.4), the subject will also be asked via IRT if he or she experienced new onset or increased pain in any major joint. If a subject responds that he or she has experienced increased pain in a major joint (Post-Baseline), the subject will be asked to rate his/her pain in that joint on the same 11-point numeric rating scale, using a 24-hour recall for the remainder of the study.

A major joint is defined as a mobile synovial joint in the limbs such as shoulders, elbows, wrists, hips, knees, ankles and excluding the joints of the toes and hands.

### 7.1.2. Subject Daily/Weekly Opioid Medication Use

Background opioid medication use will be collected in the IRT (subject diary) and in the CRF if dual concomitant opioids are used. The subject is to record dosing information pertinent to his/her ATC opioid medication and rescue opioid medication for the past 24 hours. Background opioid medication use will be assessed daily via IRT during the Pre-Treatment Period to the Week 8 Visit and then will be assessed weekly using a 24-hour recall period beginning after the Week 8 Visit through Week 24 Visit.

### 7.1.3. Concomitant NSAID Use

Use of over-the-counter or prescription NSAID use will be collected weekly via IRT from the Baseline (Day 1) visit until the Week 48 visit (or if the subject discontinues treatment, until 16 weeks after the last dose of SC study treatment). Subject is to record the number of days of NSAID use in the past week using IRT. Via telephone calls or at clinic visits, sites will interview the subject regarding their NSAID use and record the medication name, dose, and reason for use on a CRF. The investigator or designee should closely monitor for concomitant NSAID use. Subjects reporting concomitant NSAID use will be managed per guidance provided in Section 5.8.1.

## 7.2. Study Visit Efficacy Assessments and Other Instruments


### 7.2.2. Opioid-Related Symptom Distress Scale

The Opioid-Related Symptom Distress Scale (OR-SDS) is a self-administered questionnaire that assesses frequency, severity, and level of bother of opioid-associated adverse effects (refer to Appendix 11).

Pfizer developed the OR-SDS with the intent of specifically measuring the clinical benefit of the opioid-sparing treatment effect (refer to Appendix 11). The OR-SDS was derived from the Memorial Symptom Assessment Scale developed for cancer pain. The items were revised for opioid-related distress to include common adverse effects, based on literature and expert review, associated with use of opioid analgesics.

The OR-SDS will be completed by the subject via IRT during clinic visits (prior to SC dosing at dosing visits) as described in Schedule of Activities Table 1 and Table 2 and in Section 6).

### 7.2.3. Patient's Global Assessment of Cancer Pain (PGA of Cancer Pain)

The PGA of Cancer Pain is a global evaluation that utilizes a 5-point Likert scale with a score of 1 being the best (Very Good) and a score of 5 being the worst (Very Poor). Refer to Appendix 12. It is intended to provide a qualitative measurement of the subject's impression of disease activity. Refer to Appendix 12 to see the question the subject will be asked.

The PGA of Cancer Pain will be completed by the subject via IRT during clinic visits as described in Schedule of Activities Table 1 and Table 2 and in Section 6.

### 7.2.4. Eastern Cooperative Oncology Group (ECOG) Performance Status

Functional assessment tools based on performance, such as the Eastern Cooperative Oncology Group (ECOG) Performance Status,[47] are validated and widely used tools in cancer care. The ECOG Performance Status instrument is rated on a 5-point scale, with lower scores representing higher functional status. Refer to Appendix 3.

The ECOG Performance Status will be completed via IRT as described in Schedule of Activities Table 1 and Table 2 and in Section 6.


## 7.3. Safety Assessments

### 7.3.1. Cancer History

Cancer history includes primary diagnosis, date of initial diagnosis, date of initial bone metastasis and treatment history.

### 7.3.2. General Physical Examination

Each subject will undergo a general physical examination at Screening, and Weeks 24 and 48, or at Early Termination (as described in Section 6.4).

### 7.3.3. Musculoskeletal History and Physical Examination

At Screening, the investigator should collect a thorough musculoskeletal history. The investigator should inquire about current and past history of osteoarthritis, ligament tear or rupture, joint surgeries (including arthroscopic procedures), fractures, crystalline disease, osteoporosis or osteopenia, joint injuries or other conditions.

At Screening, the investigator will conduct a thorough musculoskeletal physical examination of all major joints. The musculoskeletal physical exam should evaluate the joints for swelling, redness, tenderness, deformity, osteophytes or nodes, crepitus, and pain on motion and will be documented on the CRF. The investigator should also collect subject reported information on any current joint symptoms including pain, stiffness, and swelling. Any clinically significant change in symptoms or the examination should be reported as an adverse event.

In Japan only, Post-Baseline musculoskeletal physical examinations will also be performed at the Clinic Visits indicated in Schedule of Activities Table 1 and Table 2.

### 7.3.4. Laboratory Safety Assessments

Blood and urine tests for safety assessments and/or determination of eligibility will be performed as indicated in this table and described in the subsections below:

| Chemistry | Hematology | Other | Urinalysis |
|---|---|---|---|
| Screening, Baseline, Weeks 16, 32 and 48 (or Early Termination): | Screening, Baseline, Weeks 16, 32 and 48 (or Early Termination): | Screening only: Hemoglobin A1c Serum FSH, if | Screening only (urine macro panel): |

| Chemistry | Hematology | Other | Urinalysis |
|---|---|---|---|
| Sodium,<br>potassium,<br>chloride,<br>bicarbonate,<br>glucose (non-fasting),<br>Blood Urea Nitrogen (BUN),<br>creatinine,<br>calcium,<br>phosphorus,<br>magnesium,<br>total and direct bilirubin,<br>total protein,<br>albumin,<br>cholesterol,<br>triglycerides,<br>gamma glutamyltransferase (GGT),<br>alanine aminotransferase (ALT),<br>aspartate aminotransferase (AST),<br>lactic dehydrogenase (LDH),<br>alkaline phosphatase,<br>creatine phosphokinase (CPK),<br>uric acid<br>prothrombin time (PT)<br>partial thromboplastin time (PTT) | Complete blood count with differential | applicable<br>Hepatitis screen (eg, HBsAg, Anti-HCV),<br>HIV test (HIV Ab screen)<br>Urine toxicology screen (eg, for opiates, barbiturates, amphetamines, cocaine, propoxyphene, methadone, phencyclidine, and methaqualone).<br><br><u>Screening, Week 24, 32 (or Early Termination):</u><br>Serum Pregnancy Test<br><br><u>Baseline, Weeks 8 and 16 (Pre-dose):</u><br>Urine Pregnancy Test<br><br><u>Baseline, Weeks 16, 24 and 32</u>:<br>Serum and plasma retention samples | pH,<br>protein,<br>glucose,<br>ketones,<br>blood,<br>bilirubin,<br>nitrite,<br>specific gravity and leukocytes.<br><br>Microscopic analysis performed if abnormalities are present on the above components. If urine protein by dipstick is ≥2+, then 24-hour urine collection is required for 24-hour urinary protein assessment |
| Table does not include CCI [redacted] ADA CCI [redacted]; (Refer to sections below for collection details). | | | |

### 7.3.4.1. Blood tests

Blood tests for clinical laboratory testing will be performed as described in Schedule of Activities Table 1 and Table 2. An unscheduled visit(s) may be necessary for follow-up of abnormal test results.

Refer to Section 7.3.4.3 for sample collection for serum pregnancy test and Section 7.3.4.4 for sample collection for FSH testing.

Blood samples collected for antidrug antibody (ADA), CCI [redacted] described in Sections 7.3.11 CCI [redacted]

### 7.3.4.2. Urinalysis and Urine Toxicology

Urinalysis and urine toxicology Screen will be performed at Screening by the Central Laboratory. The parameters analyzed in the urinalysis are displayed in the table above. On urinalysis, if urine protein by dipstick is ≥2+, then 24-hour urine collection will be required for 24-hour urinary protein assessment. Refer to inclusion criterion #13 and exclusion criterion #25 for renal function and toxicology-related eligibility criteria.

#### 7.3.4.3. Pregnancy Testing

For female subjects of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at the Clinic Visits indicated in Schedule of Activities Table 1 and Table 2. Serum pregnancy tests will be performed at Screening, Weeks 24 and 32 (and at Early Termination Visits 1 and 2 if applicable). Urine pregnancy tests will be performed pre-dose at Baseline, Week 8 and Week 16.

A negative pregnancy result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated as per request of institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

Qualitative urine pregnancy tests must be sensitive to at least 25 mIU/mL. Qualitative point-of-service urine pregnancy tests will be conducted with the test kit provided by the Central Laboratory in accordance with instructions provided in its package insert. Subjects who have missed a menstrual period or who show an indeterminant or positive result on the qualitative point-of-service urine test may not further progress in the study until pregnancy is ruled out using further diagnostic testing (eg, a negative quantitative serum pregnancy test conducted at a certified laboratory).

In the case of a positive hCG test, the subject will be withdrawn from study medication but may remain in the study.

Refer to Sections 6.4, 8.10 and 8.10.1 for guidance pertaining to subject withdrawal, exposure during pregnancy and additional post-natal follow-up, respectively.

#### 7.3.4.4. Serum FSH Testing

Female subjects who are not of childbearing potential and who have not had a hysterectomy or bilateral oophorectomy and who have been amenorrheic for at least 1 year with no alternative pathological or physiological cause will undergo serum FSH testing to determine post-menopausal status. A serum FSH level within the laboratory's reference range for postmenopausal females is required. Female subjects who have undergone documented total hysterectomy or bilateral oophorectomy or who have medically confirmed ovarian failure are not of childbearing potential and do not require serum FSH testing.

Female subjects who have been amenorrheic less than 1 year will be considered of child-bearing potential.

Female subjects of childbearing potential do not require serum FSH testing.

### 7.3.5. Vital Signs

Vital signs (including systolic blood pressure, diastolic blood pressure, and heart rate) will be collected as described in Schedule of Activities Table 1 and Table 2 and Section 6, after the subject has been in a sitting position for at least five minutes at each visit.

### 7.3.6. 12-Lead Electrocardiograms

12-lead ECGs will be performed as described in Schedule of Activities Table 1 and Table 2 and Section 6 for determination of ECG-related eligibility and safety monitoring.

A 12–lead ECG should be recorded after subjects have been resting at least 5 minutes in the supine position in a quiet environment. Digital ECG tracings will be performed using equipment from and analyzed by a central ECG laboratory. All standard intervals (PR, QRS, QT, QTcB, QTcF, RR intervals and HR) will be collected. The QTc interval reading produced by machine will be listed in the data listings. The QT interval will be manually measured by the Central Laboratory. The cardiologist at the central ECG laboratory reading the ECGs will be blinded regarding study drug. In the event a clinically significant ECG abnormality is seen at a visit on a post treatment ECG, the investigator should consider evaluation of the subject by a cardiologist.

Investigators will also be alerted of subjects with evidence of the following as a potential indicator of sympathetic nervous system dysfunction:

- Significant bradycardia (heart rate of ≤45 beats per minute on an ECG, exclusionary at Screening)

- Heart rate decrease from Screening of ≥25% with resulting heart rate <60 bpm.

Investigators should report adverse events of bradycardia for subjects who meet the ECG criteria listed above.

### 7.3.7. Orthostatic Blood Pressure Measurement

In addition to sitting vital sign measurements, orthostatic blood pressure measurements will be obtained using a standard manual sphygmomanometer at the clinic visits noted in Schedule of Activities Table 1 and Table 2 and Section 6. At each visit, blood pressure will be assessed in supine and standing positions. Orthostatic vital blood pressure measurements will be obtained after collection of the sitting vital signs and before any required phlebotomy. To minimize chances of orthostatic hypotension related to volume depletion, subjects should be reminded to report for clinic visits well hydrated. In this regard, investigators could consider recommending to subjects that they consume 8-16 ounces (240-480 mL) of water prior to reporting to the clinic for study visits. All orthostatic blood pressure measurements will be recorded in the IRT system.

Supine blood pressure measurement will be obtained after subjects have been in the supine position for a minimum of 10 minutes. To ensure that a stable supine blood pressure measurement is obtained, at least two systolic and diastolic measurements will be performed. If the replicate systolic and diastolic measurements differ by no more than 10 mmHg and 5 mmHg, respectively, the supine blood pressure will be considered to be stable. The mean of the two stable replicate measures will be considered to represent the Baseline supine blood pressure (mean systolic and mean diastolic blood pressure) for that visit. Once the supine blood pressure is considered to be stable, subjects will be asked to assume the standing position. After subjects have been in the standing position for 1 minute and 3 minutes,

systolic and diastolic blood pressure will be measured and recorded for both timepoints. If the measurements do not meet the criteria for orthostatic (postural) hypotension, no further measurements are needed. If either the 1 minute or 3 minute standing BP measurements show decreases meeting the criteria shown in Table 4, the sequence of supine and standing measurements should be repeated up to 2 more times. Refer to Table 4 for the criteria defining orthostatic hypotension.

**Table 4. Orthostatic Blood Pressure Changes and Orthostatic Hypotension Definition**

| Mean Supine Systolic Blood Pressure | Decrease in Blood Pressure Defining Orthostatic (postural) Hypotension | Actions |
|---|---|---|
| ≤150 mmHg<br><br>OR<br>>150 mmHg | ≥20 mmHg systolic **or** ≥10 mmHg diastolic<br><br>≥30 mmHg systolic **or** ≥15 mmHg diastolic | Repeat the sequence of measurements (supine, and standing) up to 2 times. If either the 1 minute or 3 minute standing BP meets the orthostatic (postural) hypotension criteria, then that sequence is considered positive. If 2 of 2 or 2 of 3 sequences are positive, then orthostatic hypotension is considered confirmed and the subject should be excluded from study participation |

Subjects who meet the criteria defining orthostatic hypotension as described in Table 4 at Screening or Baseline prior to randomization should be excluded from study participation. Subjects who meet criteria defining orthostatic hypotension at any post-Baseline clinic visit should follow the procedures described in Section 7.4.3.

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### 7.3.9. Radiographic Assessments

Scheduled radiographic assessments (x-rays) of the knees, hips and shoulders will be obtained as described in the Schedule of Activities Table 1 and Table 2 and Section 6.

Radiographic assessments of other major joints exhibiting signs or symptoms suggestive of osteoarthritis should also be imaged. Any joint imaged at Screening or other at-risk joints identified during the study period should also be imaged at the same intervals as the knees, hips, and shoulders.

It is recommended that the radiographs required at Screening be obtained as soon as possible after the initial Screening visit and at least two weeks prior to the Baseline visit to permit Central Reader review of the images and to establish subject eligibility for initial dosing in the study and taking into account that additional x-rays may be needed after review by the Central Reader. Subjects will not be permitted to start dosing in the study until the Screening radiographs are reviewed by the Central Reader and eligibility is established. Radiographs

required for the Week 24 visit may be conducted up to 30 days before or after the visit. Radiographs required for the Week 48 visit may be conducted up to 30 days before or after the visit. These will be preferably scheduled before the Week 48 visit but if possible, no more than 14 days after the visit. In Japan only, the Week 16 x-rays may be obtained up to 7 – 21 days before the Week 16 visit (Week 14 ± 7 days).

For subjects discontinuing prior to the Week 48 visit, follow-up radiographs of the knees, hips and shoulders should be performed as soon as possible (refer to Section 6.4) after the decision to withdraw from the study has been made, provided at least 30 days have passed since the last set of x-rays were collected. A final set of follow-up radiographs of the knees, hips and shoulders should be obtained 24 weeks (Early Termination Visit 3, Section 6.4.1.4) after the last dose of SC study treatment was administered. Any joint imaged at Screening or other at risk joints identified during the study period should also be imaged at Early Termination Visits 1 and 3.

The x-ray technologists, in addition to their professional training and certifications, will be trained in performing the radiographic protocols for the knees, hips, and shoulders for this study and given approval by Pfizer or its representative to perform study x-rays. To facilitate assessment of joint space width measurement in the knee or hip, a standardized subject and joint positioning protocol will be utilized. The Core Imaging Laboratory will be responsible for working with the sites to ensure quality, standardization and reproducibility of the radiographic images/assessments made at the Screening and follow-up time-points. Additional details regarding the required x-rays will be provided in a site imaging manual.

Central radiology readers (Central Readers) will be board certified radiologists or have the international equivalent as musculoskeletal radiologists. Central Readers will review the radiology images at Screening for assessment of eligibility including determination of identification of exclusionary joint conditions as defined in the tanezumab program imaging atlas such as osteoarthritis, rapidly progressive osteoarthritis, atrophic or hypotrophic hip osteoarthritis, subchondral insufficiency fractures, spontaneous osteonecrosis of the knee [SPONK], primary osteonecrosis, and pathological fractures. After randomization, Central Readers will review radiology images obtained for diagnosis of joint conditions that would warrant further evaluation by the Adjudication Committee such as rapidly progressive osteoarthritis, subchondral insufficiency fractures, spontaneous osteonecrosis of the knee (SPONK), primary osteonecrosis or pathological fracture.

For subjects who are identified with a possible or probable event described above and subjects undergoing total joint replacement for any reason, all images and other source documentation will be provided to the blinded tanezumab Adjudication Committee for review and adjudication of the event. The Adjudication Committee's assessment of the event will represent the final classification of the event.

#### 7.3.9.1. Radiation Exposure

The International Commission on Radiation Protection (ICRP) has developed and applied the ALARA principle in developing guidelines that balance the benefits of radiation exposures against possible risks. This principle states that human exposures to radiation should be

"**A**s **L**ow **A**s **R**easonably **A**chievable, with economic and social considerations taken into account."

Within the context of medical and research exposures, this is usually taken to mean that each individual should receive no more radiation than is necessary to obtain reliable information and that no more research participants should be irradiated than is necessary to answer a particular scientific question.

| **Radiograph** | **Annual Effective dose (mSv)** |
|---|---|
| Knee[57] | 0.036 mSv (Japan 0.048 mSv) |
| Hip[55,56] | 2.60 mSv (Japan 3.47 mSv) |
| Shoulder[55] | 0.06 mSv (Japan 0.08 mSv) |
| TOTAL | 2.696 mSv (Japan 3.598 mSv) |

The average subject exposure per radiograph is shown in the table above. The total effective dose per subject in this study from these x-rays is expected to be approximately 2.696 millisievert (mSv) (Japan 3.598 mSv). This can be compared to the annual effective dose from natural background radiation of approximately 3.0 mSv. In some cases, it is expected that a repeat image of a joint may necessary due to the quality of the initial x-ray images.

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### 7.3.11. Anti-Drug Antibody Testing (ADA)

Blood samples for the assessment of antibodies against tanezumab (ie, anti-drug antibodies; ADA) will be collected pre-dose if the collection occurs at a dosing visit. The ADA blood samples will be collected as described in Schedule of Activities Table 1 and Table 2 and Section 6.4).

Instructions regarding sample processing (eg, sample volumes, tube types, storage temperatures) will be provided in the laboratory manual.

ADA samples will be analyzed using a validated analytical method in compliance with Pfizer Standard Operating Procedures.

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The shipment address and assay lab contact information will be provided to the investigator site prior to initiation of the trial.

## 7.4. Triggered Requirements and Subject-Level Stopping Rules

The following rules will apply to individual subjects at the time of the 2nd and 3rd injection of SC study treatment.

### 7.4.1. Dysesthesia/Allodynia

Transient, resolved dysesthesia/allodynia: Administer SC study medication as planned as long as the condition has resolved before the next scheduled dose of SC study medication.

Unresolved dysesthesia/allodynia: Withhold the SC study medication for a maximum of 14 days beyond the planned dosing day to allow for resolution of the adverse event. If the dysesthesia/allodynia has not resolved within the 14 day period after the scheduled dosing date, the subject will not receive any additional doses of study medication and will enter the Early Termination Follow-Up period (refer to Schedule of Activities Table 2 and Section 6.4).

### 7.4.2. Hypersensitivity or Injection Site Reactions

If a severe hypersensitivity reaction or severe injection reaction occurs following the administration of SC study medication, study drug should be discontinued immediately and no further administrations of SC study medication will be allowed. Subjects experiencing these types of reactions will enter the Early Termination Follow-Up Period (refer to Schedule of Activities Table 2 and Section 6.4).

Severe hypersensitivity reactions are defined as those causing anaphylaxis. Severe injection site reactions are defined as those in which ulceration or severe necrosis occurs.

### 7.4.3. Orthostatic Hypotension and Sympathetic Function Adverse Events

Blood pressure changes meeting the pre-specified criteria for orthostatic hypotension and confirmed as described in Section 7.3.7 will be designated as a confirmed orthostatic hypotension episode and should be reported as an adverse event whether or not the subject had accompanying symptoms.

Confirmed episodes of orthostatic hypotension: If a confirmed episode of orthostatic hypotension occurs (as defined in Section 7.3.7) it should be reported as an adverse event and the subject should be further evaluated as described below to determine if a neurology or cardiology consultation should be obtained and/or whether further treatment with study medication should occur. Figure 2 provides a flow diagram for the processes described below.

1. If no apparent medical cause (eg, dehydration, illness, medications) is identified at the time the orthostatic hypotension criterion is met and the subject is symptomatic, the subject should be further evaluated for the presence of sympathetic autonomic neuropathy by a cardiologist or neurologist as soon as possible. See “Sympathetic function adverse events” below for decisions regarding subject management and continued dosing with study medication.

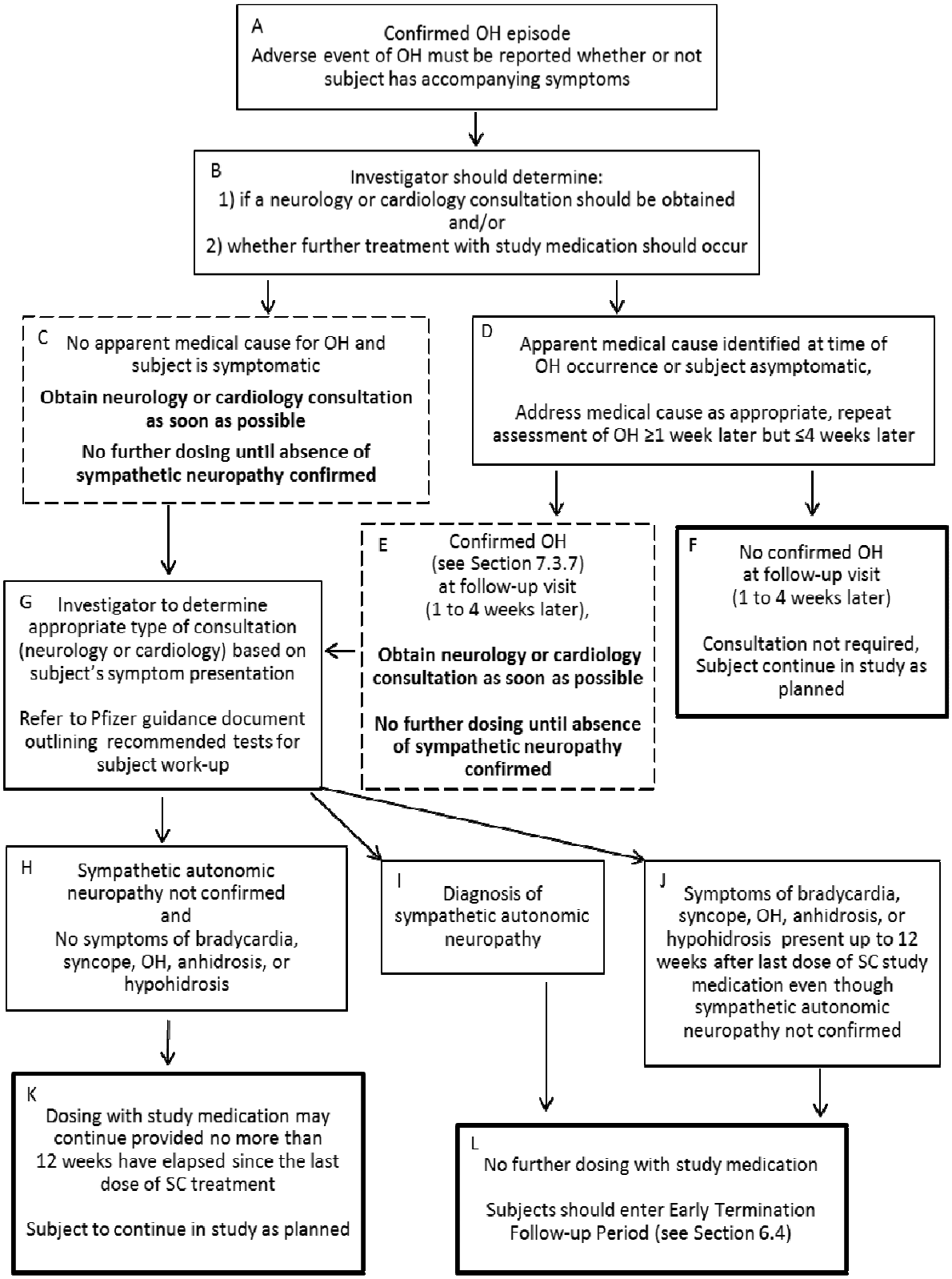
2. If an apparent medical cause is identified at the time the orthostatic hypotension criterion is met or if the subject is asymptomatic, the subject should have a repeat assessment of orthostatic hypotension performed at least 1 week later but not more than 4 weeks later. During this time the investigator should attempt to address the underlying medical cause of the orthostatic hypotension. If confirmed orthostatic hypotension (as defined in Section 7.3.7 is present at the follow-up visit, the subject should be further evaluated for the presence of sympathetic autonomic neuropathy by a cardiologist or neurologist as soon as possible. See "Sympathetic function adverse events" below for decisions regarding subject management and repeat dosing.

Sympathetic function adverse events: Subjects reporting adverse events (any seriousness or severity) with preferred terms of bradycardia (see Section 7.3.6 for ECG criteria for bradycardia), syncope, orthostatic hypotension (as described above and in boxes C and E of flow diagram Figure 2), anhidrosis or hypohidrosis should be further evaluated for the presence of sympathetic autonomic neuropathy by a cardiologist or neurologist as soon as possible.

The investigator should determine the appropriate type of consultation (neurology or cardiology) depending on the subject's symptom presentation and the investigator's assessment as to the specialist best able to evaluate the subject. Pfizer will provide a guidance document which outlines appropriate recommendations regarding tests to consider for subject work-up.

These subjects should not be dosed with SC study medication until the absence of sympathetic autonomic neuropathy has been confirmed. Subjects who are not deemed to have a sympathetic autonomic neuropathy based on this evaluation can continue the study provided no more than 12 weeks have elapsed since the last dose of SC treatment (Boxes H and K of flow diagram Figure 2). However, if the subject is still symptomatic with bradycardia, syncope, orthostatic hypotension, anhidrosis or hypohidrosis up to 12 weeks after the last dose of SC treatment, s/he should not receive additional study medication, even if a sympathetic autonomic neuropathy has not been confirmed (Boxes J and L of flow diagram Figure 2), and will enter the Early Termination Follow-Up period (refer to Schedule of Activities Table 2 and Section 6.4). Subjects found to have a sympathetic autonomic neuropathy (Boxes I and L of flow diagram Figure 2) should not receive additional study medication and will enter the Early Termination Follow-Up period (refer to Section 6.4).

**Figure 2. Follow-Up Procedures for Confirmed Orthostatic Hypotension Events**



### 7.4.4. Evaluation and Follow-Up for Increased, Severe Persistent Joint Pain

At Screening subjects will provide a daily average pain score (scored with an 11-point NRS via IRT) for the shoulders, hips and knees and any other joint for which a radiograph is obtained (refer to Section 7.1.1).

In addition, on a weekly basis beginning from Baseline through Week 48, the subject will be asked if he or she experienced new onset or increased pain in a major joint (refer to Sections 6.2.2.3 and 7.1.1.3). If a subject responds that he or she has experienced increased pain in a major joint (Post-Baseline), the subject will be asked to rate his/her pain in that joint on the same 11-point numeric rating scale, using a 24-hour recall (refer to Section 7.1.1) and will be asked to rate his/her pain in that joint for the remainder of the study.

Joint pain scores recorded electronically will be monitored by site staff to identify subjects who have a pattern of severe pain over several days or a rapid increase in pain. Subjects who record increased pain scores of severe intensity (eg, a score of 7-10 out of 10 on a numerical rating scale) in a knee, hip, shoulder or other major joint which is persistent for at least 2 weeks despite treatment with analgesic medication should be evaluated by the investigator to determine the source of the subject's pain and whether more comprehensive evaluation (eg, radiographic or MRI imaging, orthopedic consultation) of the subject is warranted. An earlier evaluation of the subject can be made at the discretion of the investigator.

At each study visit, systematic site review of the electronically recorded pain scores, and relevant spontaneously reported adverse events will be implemented. In addition, adverse events of joint pain, joint swelling, joint injury/accidents, or fractures will be evaluated by the site personnel.

Subjects meeting the criteria for increased severe or persistent pain or with other clinically significant findings based on the assessment of the investigator are considered to have joint(s) at risk and must have radiographs (x-rays) of the joint(s) obtained and sent to the Central Reader for assessment. MRI scans will not be required but may be obtained if warranted for diagnostic purposes. If warranted, the subject will be referred to an orthopedic surgeon for evaluation.

Radiographic (and any MRI) images collected as part of follow-up procedures for reports of increased severe or persistent pain or clinically significant findings of the investigator will be assessed by the Central Reader for possible or probable events of rapidly progressive osteoarthritis, subchondral insufficiency fractures (spontaneous osteonecrosis of the knee [SPONK]), primary osteonecrosis, or pathological fracture (refer to Sections 7.4.5 and 9.5).

### 7.4.5. Central Reader and Subject-Level Stopping Criteria for Possible or Probable Joint Safety Events

Subjects identified through the measures described above (in Section 7.4.4) who are determined by the Central Reader to have a possible or probable joint safety event (rapidly progressive osteoarthritis (type-1 or type-2), subchondral insufficiency fractures (spontaneous osteonecrosis of the knee [SPONK]), primary osteonecrosis, or pathological fracture), will be withdrawn from treatment and enter the Early Termination Follow-Up

period (refer to Schedule of Activities Table 2 and Section 6.4). Note: At Screening, vertebral pathologic fracture with less than 50% vertebral body destruction and no spinal canal compromise is allowable. Subjects with radiographic progression of vertebral pathologic fracture to ≥50% of the vertebral body or spinal canal compromise post-Screening will be withdrawn from treatment and enter the Early Termination Follow-Up period (refer to Schedule of Activities Table 2 and Section 6.4).

The Central Reader will review the radiology images on an ongoing basis and provide assessments to the investigator and Pfizer. For subjects who are identified with a possible or probable event described above and for subjects undergoing total joint replacement for any reason, all images and other source documentation will be provided to the blinded tanezumab Adjudication Committee for review and adjudication of the event. The Adjudication Committee's assessment of the event will represent the final classification of the event (refer to Appendix 1).

Subjects with adverse event reports of rapidly progressive osteoarthritis (type-1 or type-2), subchondral insufficiency fractures (spontaneous osteonecrosis of the knee [SPONK]), primary osteonecrosis, or pathological fracture, will be withdrawn from treatment and enter the Early Termination Follow-Up period (refer to Section 6.4).

In addition to Subject-Level Stopping Criteria for Joint Safety Events, this study will also employ Protocol-Level Stopping Criteria. Protocol-Level Stopping Criteria for Joint Safety Events are described in Section 9.7.1.

### 7.4.6. Procedures for Subjects Undergoing Joint Replacement

Subjects who have undergone or plan to undergo total joint replacement or other arthroplasty procedure during the study will be discontinued from study treatment.

Subjects who undergo total knee, hip or shoulder joint replacement surgery during the study (Double-blind Treatment Period or Follow-Up Period) will be followed for 24 weeks after the procedure as part of a separate substudy, described in Appendix 16, provided the subject consents.

Transition procedures into the substudy are determined by the timing of total joint replacement surgery:

- Subjects who have undergone or plan an immediate total knee, hip or shoulder joint replacement will be discontinued from the Double-Blind Treatment period and enter into the total joint replacement substudy. At the discontinuation visit, all procedures scheduled for the Week 24 and Week 48 visits should be completed. In addition, if the subject terminates prior to the Week 24 visit, serum and plasma retention samples should be collected, and the CCI OR-SDS, CCI and PGA instruments should be completed. Female subjects will be advised to continue their contraception regimen during a period of 112 days (16 weeks) after the last dose of SC study medication. Applicable substudy Baseline Visit activities should be completed on the same day as the Study A4091061 End of Treatment Visit.

- Subjects who plan to undergo total knee, hip or shoulder joint replacement during the study will be discontinued from the Double-blind Treatment Period and entered into Early Termination Follow-Up (See Section 6.4) until their joint replacement procedure. For these subjects, a complete early termination visit should be conducted prior to the total joint replacement (See Section 6.4) and entrance into the substudy. Substudy Baseline Visit activities should be completed on the same day as the Study A4091061 early termination visit. Subjects who have not undergone or scheduled total joint replacement surgery within the study treatment or Safety Follow-Up period of A4091061 will not be eligible for the substudy.

Subjects who undergo other types of joint replacement surgery or arthroplasty during the study should be discontinued from study treatment and complete the protocol specified Safety Follow-up Period (See Schedule of Activities Table 2 and Section 6.4), but not be entered into the substudy for follow-up after total joint replacement surgery.

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## 8. ADVERSE EVENT REPORTING

### 8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the

investigator to provide clarity and understanding of the event in the context of the clinical study.

### 8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through the end of the Safety Follow-Up period or through and including 112 calendar days after the subject's last administration of the subcutaneous investigational medication if the subject refuses the protocol defined Follow-Up period.

SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

AEs (serious and nonserious) should be recorded on the case report form (CRF) from the time the subject has taken at least 1 dose of investigational product through the last subject visit.

### 8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;

- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

### 8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error case report form (CRF) which is a specific version of the adverse event (AE) page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the adverse event (AE) page and, if applicable, any associated AE(s) are captured on an AE CRF page.

### 8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

### 8.6. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Medical device complaints may meet the SAE reporting requirement criteria (see the section on Medical Device Reporting Requirements). An incident is any malfunction (ie, the failure of a device to meet its performance specifications or to perform as intended; performance specifications include all claims made in the labeling for the device) that, directly or indirectly, might lead to or might have led to the death of a subject, or user, or of other persons, or to a serious deterioration in their state of health.

A serious injury that can cause a serious deterioration in state of health can include:

- a life-threatening illness, even if temporary in nature;
- a permanent impairment of a body function or permanent damage to a body structure;
- a condition necessitating medical or surgical intervention to prevent the above 2 bulleted items;

  Examples: clinically relevant increase in the duration of a surgical procedure, a condition that requires hospitalization or significant prolongation of existing hospitalization;

- any indirect harm as a consequence of an incorrect diagnostic or in vitro diagnostic device test results when used within the manufacturer's instructions for use;

- fetal distress, fetal death, or any congenital abnormality or birth defects.

### 8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see section on Serious Adverse Event Reporting Requirements).

### 8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin value ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 X ULN or not available;

- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

  - For subjects with preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 X ULN, or ≥8 X ULN (whichever is smaller).

  Concurrent with

  - For subjects with preexisting values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 X ULN **or** if the value reaches ≥3 X ULN (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/ international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

### 8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pre-treatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);

- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject;

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

### 8.8. Severity Assessment

| If required on the AE CRFs, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows: | |
|---|---|
| MILD | Does not interfere with subject's usual function. |
| MODERATE | Interferes to some extent with subject's usual function. |
| SEVERE | Interferes significantly with subject's usual function. |

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

### 8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and nonserious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see the section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

### 8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

2. An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

3. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on a serious adverse event (SAE) Report Form and an Exposure During Pregnancy (EDP) supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs.

- Additional information about pregnancy outcomes that are reported as SAEs follows:
- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

### 8.10.1. Additional Postnatal Development Follow-Up

The investigator will be asked to assist with collection of assessments of postnatal development as part of a separate protocol. Participation in that protocol is optional and will require that the subject review, agree and sign a separate informed consent document specific to that study, explaining the details of the post-partum follow-up for the subject and the newborn to participate in these assessments of postnatal development.

## 8.11. Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an adverse event.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE eport form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a Case Report Form (CRF), however a copy of the completed SAE report form is maintained in the investigator site file.

## 8.12. Withdrawal Due to Adverse Events (See Also the Section on Subject Withdrawal/Early Termination)

Withdrawal due to AE should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

## 8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

## 8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

### 8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

### 8.14.2. Nonserious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

### 8.14.3. Medical Device Reporting Requirements

All medical device complaints regardless of whether the medical device complaint is associated with an AE will be collected on the applicable pages within the CRF. This includes potential incidents or malfunctions associated with the use of a medical device

product. An incident or malfunction is an event that might have led to death or serious deterioration in health, or if it occurred again might have led to death or serious deterioration in health.

Pfizer is to be notified of all medical device complaints within 24 hours of the investigator's awareness of the event.

Refer to the Pharmacy Manual for procedures for forwarding medical device complaints not associated with an SAE to Pfizer.

### 8.14.4. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

## 9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

### 9.1. Sample Size Determination

The primary efficacy endpoint is the change from Baseline to Week 8 in the average daily pain intensity in the index bone metastasis cancer pain site measured by the 11-point Pain Intensity NRS.

From a prior study (A4091003), the assumed within-group standard deviation for the change from Baseline in the Average Pain NRS is 2.0. The targeted mean treatment difference for tanezumab 20 mg SC + opioids versus placebo + opioids is -1.0. A Group Sequential Design with a single interim analysis will be used for the assessment of futility and efficacy of the primary efficacy parameter (refer to Section 9.6 for details).

The interim analysis will be performed when at least 50% (36 from each treatment group) of subjects have completed or discontinued prior to Week 8. Based on current enrollment, it is expected that the interim analysis will include approximately 36 to 45 subjects per treatment group.

Based on data from the previous cancer pain study (A4091003), and not accounting for the assessment of futility and efficacy at the interim analysis, a sample size of approximately 72 subjects per treatment group is required to achieve 85% power to demonstrate statistical significance (using the 2-sided 5% significance level), in the treatment comparison of tanezumab 20 mg + opioid versus placebo + opioid. Taking into account for the assessment of non-binding futility and efficacy at the interim analysis, the same sample size is expected to achieve 80 to 85% power.

## 9.2. Efficacy Analysis

Efficacy data from subjects randomized to the tanezumab 10 mg treatment group will be summarized but not included in analyses of efficacy.

### 9.2.1. Primary Endpoint Analysis

The primary efficacy endpoint is the change from Baseline to Week 8 in the daily average pain intensity in the index bone metastasis cancer pain site measured by the 11-point Pain Intensity Numerical Rating Scale (NRS), where scores range from 0-10.

Baseline is defined as the mean average daily Pain NRS score during the Baseline Assessment Period prior to Randomization (expected to be 5 days). The Week 8 pain intensity value is the mean of the daily average Pain intensity scores for the 7 days prior to the Week 8 visit. If any of the seven Week 8 daily scores are missing then the Week 8 value will be calculated over the remaining observations.

The primary efficacy endpoint will be analyzed using an ANCOVA model, with model terms for Baseline score, the stratification variables, Baseline opioid use, region and treatment group. The stratification variables are (i) tumor aggressiveness (assessed by Eastern Cooperative Group [ECOG] performance status and (ii) presence/absence of concomitant anticancer treatment (eg, chemotherapy or hormonal therapy or anti-hormonal therapy).

The primary analysis of the primary endpoint will use multiple imputation for missing data, to account for uncertainty around the unobserved subject response. The basis for imputing missing values will be dependent on the reasons for missing data. For subjects with missing data due to discontinuation prior to Week 8 for lack of efficacy, or for an adverse event or death, imputation will be based on sampling from a normal distribution using a mean value equal to the subject's Baseline efficacy value and the standard deviation (over the placebo and tanezumab 20 mg treatment groups) of the observed efficacy data at Week 8. For subjects with missing data for any other reason, imputation will be based on sampling from a normal distribution using a mean value equal to subject's last observed efficacy value and standard deviation (over the placebo and tanezumab 20 mg treatment groups) of the observed efficacy data at Week 8. Imputed values will be truncated at 0 and 10, but not rounded. One hundred imputation samples will be used, and the ANCOVA model described above will be used for each imputation dataset. The final results will be calculated using the combined sets of results from each imputation dataset analysis.

The significance level for the primary analysis of the primary endpoint at the interim and the final analysis will be determined in a way to have an overall two-sided 5% significance across analyses. The boundary to declare efficacy at the interim or the final analysis will be determined using the Lan-DeMets alpha spending function with the O'Brien-Fleming style boundary (refer to Section 9.6 for details). The non-binding futility stopping rule will not influence the efficacy boundary.

The primary efficacy population (Intent to Treat Set) is defined as all randomized subjects who received the Day 1 SC injection (either tanezumab SC or matching placebo SC). A

secondary efficacy population (Per-Protocol) is defined as all subjects in the Intent to Treat Set who were not major protocol deviators.

### 9.2.2. Secondary Efficacy Endpoint Analysis

Unless otherwise stated, all data up to Week 24 will be summarized, and data for the specified time points up to Week 24 will be analyzed.

The change from Baseline for the daily average and worst pain intensity in the bone metastasis index cancer pain site will be summarized for each week from 1 to 24. The change from Baseline to Weeks 1, 2, 4, 6, 8 (Worst Pain), 12, 16 and 24 will be analyzed using analysis of covariance (ANCOVA) as described above, using multiple imputation.

A secondary analysis for the change from Baseline in the daily average pain scores will use a repeated measures mixed effects model, on the available data over Weeks 1 to 24. Estimates for treatment groups and treatment difference for Weeks 1, 2, 4, 6, 8, 12, 16 and 24 will be shown. Additional secondary analysis for the change from Baseline to Week 8 and 16 in the daily average pain will use single imputation Last Observation Carried Forward (LOCF) and Baseline Observation Carried Forward (BOCF) for missing data.

The mean of the subject's average and worst pain in the non-index cancer sites, over all non-index sites (for up to 2 sites per subject) and for visceral non-index cancer sites will be calculated for Baseline and for each week, and for the change from Baseline. The change from Baseline to Weeks 1, 2, 4, 6, 8, 12, 16 and 24 in average and worst pain in the non-index cancer pain sites will be analyzed using analysis of covariance (ANCOVA) as described above, using multiple imputation. An additional analysis will utilize only those sites where Baseline average/worst pain is at least 5. If a subject has no nominated non-index sites (first analysis) or no nominated non-index sites where Baseline is at least 5 (second analysis) then that subject would be excluded from the respective analysis.

Additional ANCOVA analyses with multiple imputation for the primary endpoint will be used to examine the interaction of treatment group with study site, Baseline pain score, type of primary cancer (eg, breast, lung, etc), Baseline opioid use and the stratification parameters.

The change from Baseline to Weeks 2, 4, 8, 16, and 24 in the CCI [redacted] CCI will also be summarized, and analyzed using the ANCOVA main effects model as described above with multiple imputation.

For the daily worst and average pain (in the index site) response efficacy endpoints (defined by a ≥30%, ≥50%, ≥70% and ≥90% change from Baseline to Weeks 1, 2, 4, 6, 8, 12, 16 and 24), will be summarized and analyzed using logistic regression for binary data, with model terms for Baseline average/worst pain subscale score, stratification variables, and treatment group. Imputation for missing data will use both LOCF and BOCF, where imputation with BOCF will lead to the subject being assessed as a non-responder for the response endpoint at a particular time point. Also, in order to closely match the primary imputation analysis, a mixed BOCF/LOCF imputation for response endpoints will be used. In this analysis BOCF imputation (ie, a subject would be a non-responder) would be used for missing data due to

discontinuation for the reasons of lack of efficacy, adverse event, or death up to the time point of interest, and LOCF imputation would be used for missing data for any other reason.

The proportion of subjects who have a reduction from Baseline to Weeks 8 and 16 in average and worst pain of >0%, ≥10% to ≥90% (in steps of 10%), and =100% (ie, average/worst pain is 0) will be tabulated and plotted. This will be shown using observed cases, and mixed BOCF/LOCF as described above for missing data.

The change from Baseline to Weeks 2, 4, 8, 16 and 24 in the Patient Global Assessment of Cancer Pain will be summarized by treatment group, and analyzed using ANCOVA as described above with multiple imputation. A second analysis of this parameter will use Cochran-Mantel-Haenszel test for the change from Baseline to Weeks 2, 4, 8, 16 and 24.

The response parameter of an improvement of ≥2 in the Patient Global Assessment of Cancer Pain will be analyzed as described above for the daily average and worst response parameters using mixed BOCF/LOCF as described above for missing data (using the covariates of Baseline Patient Global Assessment of Cancer Pain and Baseline daily average pain).

A table showing number and percentage of subjects will summarize the response for each dimension (item) of the CCI at Baseline and Weeks 8, 16 and 24. These summary tables will be shown by treatment group. In addition, for each treatment and each time point assessed, descriptive statistics (mean, standard deviation, median, number of subjects) will characterize the five-item health status profile on the CCI in terms of the health utility score and the EQ-VAS.

CCI

CCI

### 9.3.4. Opioid Use and Opioid Adverse Effects Analysis

Opioid data from subjects randomized to the tanezumab 10 mg treatment group will only be summarized, and not included in statistical analyses of opioid use data.

Average daily opioid consumption (mg of morphine equivalent dosage) and average number of doses of rescue opioid consumption per week will be summarized for each week up to Week 24. Percent change from Baseline in average daily opioid consumption will be analyzed using ANCOVA on the rank scores with treatment and the stratification variables as factors. The average number of doses of rescue opioid consumption per week will be analyzed using a negative binomial model taking into account Baseline daily average pain and Baseline opioid use.

The number of doses of rescue medication per week will be summarized by treatment group for each week up to Week 24. The total number of doses of rescue medication in Weeks 1, 2, 4, 8, 16, and 24 will be analyzed using a negative-binomial regression model using the log-total number of days of data collection as the subject offset variable. The resulting analysis will show the estimated rate of opioids taken as rescue medication for each week. This estimated rate will be shown by treatment group with standard error and 95% CI. The ratio of the opioid usage rate between tanezumab + opioid versus opioid alone will be shown (with standard error and 95% CI).

The Opioid-Related Symptom Distress Scale (OR-SDS) is a questionnaire on the frequency, severity and level of bother of 10 symptoms. For each symptom the mean of the frequency, severity and bother is calculated to become the Multi-Domain Average (MDA). These are the four dimensions for each symptom. The mean of each dimension over all symptoms is calculated to become the frequency, severity, bother and MDA composite scores. Each of the four dimensions will be summarized by treatment and treatment difference for the 10 symptoms and the overall composite, a total of 44 sets of summary measures. The MDA for each symptom and the four dimensions for the composite score will be analyzed for each time point. The analysis of this data will use a mixed effects repeated measures model and show analysis results for the change from Baseline to Weeks 2, 4, 8, 16, and 24.

## 9.4. Safety Analysis

Adverse events, concomitant medications, laboratory safety tests, physical and CCI CCI vital signs, ECGs, the anti-drug antibody test will be collected for each subject during the study according to the Schedule of Assessments. Standard safety reporting tables will summarize and list the safety data.

Safety data from subjects randomized to the tanezumab 10 mg treatment group will be included in safety summaries and listings.

Adverse Events of Abnormal Peripheral Sensation will be summarized. CCI CCI

Separate adverse event summaries by treatment group for adverse events of decreased sympathetic function will be conducted. More specifically, adverse events with the

following preferred terms will be considered to represent adverse events of decreased sympathetic function: Blood pressure orthostatic decreased, bradycardia, dizziness postural, heart rate decreased, orthostatic hypotension, presyncope, sinus bradycardia, syncope, anhidrosis, hypohidrosis, abdominal discomfort, diarrhea, early satiety, fecal incontinence, nausea, vomiting, ejaculation delay, ejaculation disorder, ejaculation failure, hypertonic bladder, micturition urgency, nocturia, urinary frequency, urinary hesitation, urinary incontinence, respiratory distress and respiratory failure. If necessary, this list of preferred terms may be adjusted for updates made to the MEDICAL DICTIONARY FOR DRUG REGULATORY AFFAIRS (MedDRA) dictionary versions used for reporting.

In addition to summaries of adverse events considered to represent adverse events of decreased sympathetic function noted above, adverse events of syncope, bradycardia, orthostatic hypotension, anhidrosis, or hypohidrosis are designated as adverse events of interest that will be reviewed by the unblinded E-DMC (refer to Section 9.7).

Selected adverse events of interest and common adverse events will be summarized using Risk Differences (with 95% confidence intervals) between the tanezumab 20 mg group and placebo. In addition, significance testing will be performed for adverse events of interest between the tanezumab 20 mg group and placebo. There will be no multiplicity adjustment for these significance tests.

Incidence of orthostatic hypotension using postural changes in blood pressure, in addition to mean changes in postural blood pressure will be summarized.


A listing of the subjects who develop anti tanezumab antibodies after treatment for each dose, and the proportion of subjects who develop anti tanezumab will be summarized for each dose.

The PK profile will be examined for subjects with anti tanezumab antibodies.

Individual subjects with positive ADA results will be evaluated for potential impact on the individual's pharmacokinetic, efficacy and safety profile.

### 9.5. External Adjudication Committee

A blinded Adjudication Committee consisting of external experts in orthopedic surgery, rheumatology, orthopedic pathology, or radiology with expertise in subjects with end stage

osteoarthritis and osteonecrosis will be convened. The Adjudication Committee will have written operating procedures and a Charter, including a specific description of the scope of their responsibilities. In general, the Adjudication Committee will be asked to review all joint-related safety events resulting in total joint replacement and/or discontinuation from the study as well as adverse events reported as osteonecrosis, rapidly progressive osteoarthritis, or other events suggestive of abnormal joint destruction. These will include, but will not be limited to events identified for adjudication by the Central Reader (refer to Section 7.3.9). Refer to Appendix 2 for adjudication categories and conditions that could result based on a subject's case assessment by the Adjudication Committee.

Prior to the Adjudication Committee's review of a given event, the Committee will be provided with blinded, available source documentation of progress reports from the investigator, orthopedic consult reports, operative reports, radiology reports, pathology reports, x-ray images, MRI images, and pathology specimens for review. Copies of all relevant clinical information including the items listed above should be provided to Pfizer or its designee for review by the external Adjudication Committee. Copies of the information should include the study number, site number and subject number, but it should not include the subject's name or initials.

After each review meeting, the Adjudication Committee's blinded summary of events will be provided to the External Data Monitoring Committee (E-DMC).

### 9.6. Interim Analysis

The study is designed as a Group Sequential Design using a single interim analysis. The purpose of the interim analysis is to assess the non-binding futility and the evidence of efficacy of the primary efficacy parameter.

The interim analysis will be performed when at least 50% (36 from each treatment group) of subjects have completed or discontinued prior to Week 8. Based on current enrollment, it is expected that the interim analysis will include approximately 36 to 45 subjects per treatment group.

The non-binding futility stopping boundary will be defined using EAST version 6.3.1 (Cytel inc.), using the conditional power of 10% (based on estimated delta/sigma) boundary, for a one-sided assessment of futility. The efficacy stopping boundary will be defined using the same software, using the Lan-DeMets Beta alpha spending function with the O'Brien-Fleming style boundary, for a one-sided assessment of efficacy.

The analysis will be conducted by a statistician outside of Pfizer, with all details of the treatment allocation, analysis and results unknown to all within Pfizer or the contract research organization (CRO) performing the final analysis programming. In the situation where the futility or efficacy stopping rule is met, then the statistician will convey the results of the interim analysis to a senior statistician within Pfizer (but outside the study team) to repeat and ratify the analysis. The decision to stop the study will be made by Pfizer. Results of the interim analysis will not be known to anybody in the study team until the formal unblinding of the study at database lock.

Before any interim analysis is initiated, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind as per Pfizer's standard operating procedures (SOPs) will be documented and approved in an Interim Analysis charter. In addition, the analysis details must be documented and approved in an interim analysis SAP or final SAP.

Once all subjects have completed the Week 24 Visit, a data-cut may be produced, and the study may be reported for efficacy data. This would be an unblinded analysis of the final efficacy data, although patients and investigators would remain blinded throughout the remainder of the trial. Safety data would continue to be collected for the remaining subjects in the trial, up to the end of Week 48. A final analysis of safety data would also be produced for all subjects for the total study duration. Any joint safety events will continue to be adjudicated in a blinded manner.

### 9.7. Data Monitoring Committee

This study will use an External Data Monitoring Committee (E-DMC) which has been instituted for the tanezumab clinical program.

This committee will be composed of at least one rheumatologist, neurologist, statistician, and epidemiologist. The E-DMC will review unblinded safety data including (but not limited to) adverse events and serious adverse events on a regular basis throughout the trial. Adverse events of syncope, bradycardia, orthostatic hypotension, anhidrosis or hypohidrosis along with other adverse events that are possibly related to the sympathetic nervous system will be monitored by the E-DMC during review of unblinded safety data. The E-DMC will have written operating procedures and a Charter, including a specific description of the scope of their responsibilities.

The E-DMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the Charter. If the blinded Adjudication Committee identifies adjudicated events of rapidly progressive osteoarthritis type 2, subchondral insufficiency fracture (spontaneous osteonecrosis of the knee [SPONK]), primary osteonecrosis or pathological fracture, occurring at a rate that could trigger the protocol-based stopping criteria, an urgent, ad hoc assessment of the events will be made by the E-DMC.

Any recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

Pfizer Standard Operating Procedures regarding periodic safety reviews by the study team and the Tanezumab Risk Management Committee will be followed. This committee will be composed of members inside and outside the immediate study team who will review blinded safety data from individual studies as well as data pooled across the studies on an ongoing basis. A safety review plan will be in place governing the frequency and extent of safety review.

### 9.7.1. Protocol-Level Rules for Dosing Suspension/Safety Assessments

#### 9.7.1.1. Serious Adverse Events

Tanezumab safety will be reviewed at two levels; blinded data reviews by Pfizer and unblinded reviews by the E-DMC. The E-DMC will review unblinded safety data including adverse events and serious adverse events on a regular basis throughout the course of these studies. Pfizer performs blinded review of all serious adverse event data (including those serious adverse events specified below) and a cumulative review on a monthly basis. If blinded review notes a pre-specified serious adverse event occurring at a rate that could trigger the protocol-based dosing suspension rule (ie, at least 3 or more cases of a given pre-specified serious adverse event), an urgent, ad hoc assessment by the E-DMC will be conducted. The E-DMC will determine whether a protocol-based dosing suspension rule should be triggered. At the individual protocol-level, if a given pre-specified serious adverse event is reported in 3 more subjects in any individual tanezumab treatment group than for placebo-treated subjects, the protocol-based rule for dosing suspension will be triggered.

The pre-specified serious adverse events are:

- Sudden cardiac death or cardiac death;
- Acute renal failure;
- Anaphylactic shock or severe anaphylactic reaction;
- Neuropathic joint or neuropathic arthropathy (ie, Charcot joint);
- Autonomic or peripheral neuropathy confirmed with objective findings such as treatment-emergent abnormalities on CCI nerve conduction abnormalities or biopsy findings consistent with peripheral neuropathy.

If a protocol-based rule for dosing suspension is triggered, it will result in suspension of further dosing of subjects in the study until a decision is reached regarding whether it is safe to resume dosing in some or all treatment groups or whether the study should be terminated completely. This decision will be made by the sponsor in consultation with the tanezumab E-DMC. Factors that may be considered in making this decision in relation to serious adverse events or adjudicated clinically significant adverse events include:

- Consideration of relationship of study medication to the adverse event;
- Consideration of whether similar adverse events are occurring in other tanezumab studies with similar subject populations;
- Dosage of tanezumab (10 mg or 20 mg) and distribution of adverse events across tanezumab dose arms;
- Possible differences in the Baseline demographics between treatment groups;
- Use of concomitant medications;

- Possible differences in Baseline medical history;
- Study medications other than tanezumab;
- Duration of therapy (0-6 months, 6-12 months).

#### 9.7.1.2. Events consistent with Hy's Law

- If two events are reported which are consistent with Hy's Law in tanezumab-treated subjects, irrespective of dose across all ongoing tanezumab studies, dosing will be temporarily suspended in all studies until the relationship to study drug is established. If two events consistent with Hy's Law are considered to be related to treatment with tanezumab or the cause cannot be determined, all dosing in the pain program may be stopped.

#### 9.7.1.3. Joint Safety Events

If the blinded Adjudication Committee identifies adjudicated events of rapidly progressive osteoarthritis type 2, subchondral insufficiency fractures (or spontaneous osteonecrosis of the knee [SPONK]), primary osteonecrosis, or pathological fracture, occurring at a rate that could trigger the protocol-based stopping criteria, an urgent, ad hoc assessment of the events will be made by the External Data Monitoring Committee (E-DMC).

The protocol (or treatment group) stopping rule will be based on the assessment of the number of subjects with adjudicated events of interest (rapidly progressive osteoarthritis type 2, subchondral insufficiency fractures (or spontaneous osteonecrosis of the knee [SPONK]), primary osteonecrosis, or pathological fracture) during the course of the study. Assuming the rate of adjudicated events in the placebo group is no more than 6 per 1000 patient-years, if adjudicated events of interest are reported in 3 or more subjects in any tanezumab treatment group than for the placebo treatment group, a treatment-group or protocol-based stopping rule will be triggered. If the rate of events in the placebo treatment group is higher than 6 per 1000 patient-yrs the appropriate threshold number of events for the stopping rule will be reassessed. If the protocol-based stopping rule is triggered, the E-DMC will formulate a recommendation whether it is safe to continue dosing in some or all treatment groups or whether the study should be terminated completely. This decision will be made by Pfizer in consultation with the E-DMC.

## 10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance

audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

## 11. DATA HANDLING AND RECORD KEEPING

### 11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital’s or the physician's subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator’s site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

### 11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed

consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the International Conference on Harmonisation (ICH) guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

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

## 12. ETHICS

### 12.1. Institutional Review Board (IRB)/Ethics Committee (EC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

### 12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 and 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

### 12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data is compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code based on a numbering system provided by Pfizer in order to de-identify study subjects. The study site will maintain a confidential list of subjects who participated in the study linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

Given the design of this study, which includes a 24 week safety followup period during which subjects no longer receive study medication and instead receive standard-of-care treatment, providing additional investigational product at the conclusion of the study is not feasible.

### 12.4. Subject Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

### 12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

# 13. DEFINITION OF END OF TRIAL

## 13.1. End of Trial in a Member State

End of trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of subjects have been recruited and completed the study as stated in the regulatory application (ie, CTA) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

## 13.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as database lock.

# 14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of tanezumab at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 1 week. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

# 15. PUBLICATION OF STUDY RESULTS

## 15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for all Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

*Primary completion* date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome,

whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

### 15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

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## Appendix 1. List of Abbreviations

| This is a list of abbreviations that may or may not be used in the protocol. | |
|---|---|
| **Abbreviation** | **Term** |
| ACR | American College of Rheumatology |
| ADA | anti-drug antibody |
| AE | adverse event |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| ANCOVA | analysis of covariance |
| ASA | American Society of Anesthesiologists |
| AST | aspartate aminotransferase |
| ATC | around-the-clock |
| BL | Baseline |
| BMI | body mass index |
| BOCF | Baseline Observation Carried Forward |
| BP | blood pressure |
| BAP | Baseline Assessment Period |
| CCI [redacted] | |
| BUN | blood urea nitrogen |
| CCI [redacted] | [redacted] |
| COX-2 | cyclooxygenase-2 |
| CPK | creatine phosphokinase |
| CRF | case report form |
| CRA | Clinical Research Associate |
| CRO | Contract Research Organization |
| CCI [redacted] | [redacted] |
| CSA | clinical study agreement |
| CT | computerized tomography |
| CTA | clinical trial application |
| CTS | carpal tunnel syndrome |
| CCI [redacted] | [redacted] |
| DU | dispensable unit |
| EC | ethics committee |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| E-DMC | External Data Monitoring Committee |
| EDP | exposure during pregnancy |
| EDTA | edetic acid (ethylenediaminetetraacetic acid) |
| CCI [redacted] | |
| ER | extended release |
| ESR | erythrocyte sedimentation rate |

| | |
|---|---|
| EU | European Union |
| EudraCT | European Clinical Trials Database |
| FDA | Food and Drug Administration (United States) |
| FDAAA | Food and Drug Administration Amendments Act (United States) |
| FSFV | first subject first visit |
| FSH | follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| GGT | gamma glutamyltransferase |
| GnRH | gonadotropin-releasing hormone |
| hCG | human chorionic gonadotropin |
| HIV | human immunodeficiency virus |
| HR | heart rate |
| CCI | [redacted] |
| ICH | International Conference on Harmonisation |
| ICRP | International Commission on Radiation Protection |
| CCI | [redacted] |
| ID | identification |
| IND | Investigational New Drug application |
| INR | International Normalized Ratio |
| IgG | immunoglobulin G |
| IgG2 | immunoglobulin G Type 2 |
| IRB | institutional review board |
| IL | interleukin |
| CCI | [redacted] |
| IR | immediate release |
| IRT | interactive response technology |
| ITT | intent to treat |
| IUD | intrauterine device |
| IUS | intrauterine system |
| IV | intravenous |
| IWRS | interactive web response system |
| LDH | lactate dehydrogenase |
| LFT | liver function test |
| LOCF | Last Observation Carried Forward |
| LSLV | last subject last visit |
| LSMean | least squared mean |
| MAb 911 | murine precursor antibody to tanezumab |
| MDA | Multi-Domain Average |
| CCI | [redacted] |
| MMR | measles, mumps and rubella |
| MRI | magnetic resonance imaging |
| mSv | millisievert |
| N/A | not applicable |
| NCCN | National Comprehensive Cancer Network |
| NGF | nerve growth factor |

| | |
|---|---|
| NGFI | nerve growth factor inhibitor |
| CCI | [redacted] |
| NRS | numeric rating scale |
| NSAID | non-steroidal anti-inflammatory drug |
| NYHA | New York Heart Association |
| OA | osteoarthritis |
| CCI | [redacted] |
| OR-SDS | Opioid-Related Symptom Distress Scale |
| OTC | over-the-counter |
| PCD | primary completion date |
| PD | pharmacodynamic |
| PET | positron emission tomography |
| PFS | pre-filled syringe |
| PGA | Patient's Global Assessment |
| CCI | [redacted] |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| PT | prothrombin time |
| PTT | partial thromboplastin time |
| QT | in electrocardiography, the time corresponding to the beginning of depolarization to repolarization of the ventricles |
| QTc | in electrocardiography, the time corresponding to the beginning of depolarization to repolarization of the ventricles, corrected for heart rate |
| QTcB | QT corrected for heart rate using Bazett's formula |
| QTcF | QT corrected for heart rate using Fridericia's formula |
| CCI | [redacted] |
| RPOA | rapidly-progressive osteoarthritis |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SAPS | Self-Administered Patient Satisfaction Scale |
| CCI | [redacted] |
| SC | subcutaneous |
| SNRI | serotonin norepinephrine reuptake inhibitor |
| SOA | schedule of activities |
| SOP | Standard Operating Procedure |
| CCI | [redacted] |
| SPADI | Shoulder Pain and Disability Index |
| SPONK | spontaneous osteonecrosis of the knee |
| SRSD | single reference safety document |
| Tan | tanezumab |
| TNF-α | tumor necrosis factor alpha |
| trkA | tropomyosin receptor kinase A |
| ULN | upper limit of normal |
| UK | United Kingdom |
| US | United States |

| | |
|---|---|
| VAS | visual analog scale |
| WHO | World Health Organization |
| WOMAC | Western Ontario and McMaster University Osteoarthritis Index |

## Appendix 2. Adjudication Categories

| Adjudication Category | Adjudicated Condition |
|---|---|
| 1 | Primary Osteonecrosis |
| 2 | Worsening Osteoarthritis |
| 2a | Rapidly Progressive Osteoarthritis (type-1 or type-2) |
| 2b | Normal progression of osteoarthritis |
| 2c | Not enough information to distinguish between rapidly progressive osteoarthritis and normal progression of osteoarthritis |
| 3 | Subchondral insufficiency fracture |
| 4 | Pathologic fracture |
| 5 | Other (with diagnosis specified) |
| 6 | Not enough information to specify a diagnosis |

## Appendix 3. Eastern Cooperative Group (ECOG) Performance Status

ECOG Performance Status[47]

| Grade | ECOG Performance Status Definition |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physical strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work. |
| 2 | Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours. |
| 4 | Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair. |
| 5 | Dead. |

## Appendix 4. American College of Rheumatology (ACR) Classification Criteria for Osteoarthritis

### 1986 Osteoarthritis Knee Criteria[53]

Clinical and radiographic criteria for classification of idiopathic osteoarthritis of the knee.

Meets criteria 1, 2 and 3:

1. Knee pain;
2. Presence of at least 1 of the following 3:
    - Age greater than 50 years;
    - Morning stiffness less than 30 minutes in duration;
    - Crepitus.
3. Presence of osteophytes on x-ray.

### Osteoarthritis Hip Criteria[54]

Combined clinical (history, physical examination, laboratory) and radiographic criteria for osteoarthritis of the hip, traditional format.

1. Hip pain;
2. AND at least 2 of the 3 following features:
    - Erythrocyte sedimentation rate (ESR) less than 20 mm/hour;
    - Radiographic femoral or acetabular osteophytes;
    - Radiographic joint space narrowing (superior, axial, and/or medial).

ESR testing may be conducted at the local laboratory or at the study site by appropriately-trained staff using an approved test kit; prior ESR test results from a local laboratory may also be used provided they have been performed within 30 days of Screening.

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## Appendix 6. American Society of Anesthesiologists (ASA) Physical Status Classification

**ASA Physical Status Classification**

The ASA physical status classification system is used for assessing the fitness of patients before surgery. In 1963 the American Society of Anesthesiologists (ASA) adopted the five-category physical status classification system; a sixth category was later added. These are:

1. A normal healthy patient
2. A patient with mild systemic disease
3. A patient with severe systemic disease
4. A patient with severe systemic disease that is a constant threat to life.
5. A moribund patient who is not expected to survive without the operation.
6. A declared brain-dead patient whose organs are being removed for donor purposes.

## Appendix 7. Half-Lives of NSAIDs and Other Analgesics

Other than background opioids (refer to Section 5.8.2.1) and certain permitted non-opioid analgesics (refer to Section 5.8.2.2), the use of any other analgesic is prohibited throughout the study, beginning 48 hours prior to the start of the Baseline Assessment Period (the five days prior to Randomization/Baseline) or at the period of time prior to the start of the Baseline Assessment Period that is at least 5 times the half-life of the particular analgesic used, whichever is greater. Half-lives of the analgesics included below are shown for reference and do not mean that it is prohibited, unless it is described in Section 5.8.1.1. Note that a stable regimen of aspirin taken for cardiac prophylaxis at a dose of ≤325 mg/day is permitted throughout the study.

These lists are not all-inclusive. The Physician's Desk Reference provides half-life information.

| **HALF-LIVES OF NSAIDs AND OTHER ANALGESICS** | | |
|---|---|---|
| **Analgesic** | **Half-life (hours)** | **Minimum Washout Period** |
| Aspirin >325 mg/day | 0.25 | 2 days |
| Azapropazone | 15.0 | 4 days |
| Bromfenac | 1.3-3.1 | 2 days |
| Capsaicin (cream, ointments, patches) | 2.0 | 2 days |
| Carprofen | 12.0 | 3 days |
| Celecoxib | 11.0 | 3 days |
| Codeine | 3.5 | 2 days |
| Diclofenac | 1.1 | 2 days |
| Diclofenac/misoprostol | 2.4-9.0 | 2 days |
| Diflunisal | 13.0 | 3 days |
| Dipyrone | 2.0-5.0 | 2 days |
| Etodolac | 6.0 | 2 days |
| Fenbufen | 11.0 | 3 days |
| Fentanyl | Contact study clinician | |
| Fenoprofen | 2.5 | 2 days |
| Flufenamic acid | 1.4 | 2 days |
| Flurbiprofen | 3.8 | 2 days |
| Hydrocodone | 4.5 | 2 days |
| Ibuprofen | 2.1 | 2 days |
| Indomethacin | 4.6 | 2 days |
| Ketoprofen | 1.8 | 2 days |
| Ketorolac | 4.0-9.0 | 2 days |

| **HALF-LIVES OF NSAIDs AND OTHER ANALGESICS** | | |
|---|---|---|
| Lidocaine patch or EMLA (lidocaine/prilocaine) | 2.0 | 2 days |
| Meclofenamate | 2.0-4.0 | 2 days |
| Mefenamic acid | 2.0 | 2 days |
| Meloxicam | 16.0 to 20.0 | 5 days |
| Meperidine | 3.7 | 2 days |
| Mexiletine | 6.0-17.0 | 4 days |
| Nabumetone | 26.0 | 6 days |
| Naproxen | 14.0 | 3 days |
| Oxaprofen | 40.0-50.0 | 11 days |
| Oxaprozin | 58.0 | 13 days |
| Oxycodone | 3.2 | 2 days |
| Oxycodone CR | 8.0 | 2 days |
| Phenylbutazone | 68.0 | 15 days |
| Piroxicam | 57.0 | 12 days |
| Pirprofen | 3.8 | 2 days |
| Propoxyphene | 12.0 | 3 days |
| Salicylates | 2.0-15.0 | 4 days |
| Sulindac | 14 | 3 days |
| Suprofen | 2.5 | 2 days |
| Tenoxicam | 60.0 | 13 days |
| Tiaprofenic acid | 3.0 | 2 days |
| Tolmetin | 1.0 | 2 days |
| Tramadol | 5.9 | 2 days |
| Diclofenac gels | 1.9 | 2 days |

## Appendix 8. Restrictions on Prior and Concomitant Medications

Medications for non-cancer, non-pain conditions are permitted throughout the study. Dose adjustments (including starting a new therapy) during the study can be made if required, and recorded on the concomitant medication CRF.

Some restrictions apply to certain prior and concomitant medications including those used in the treatment of the underlying cancer, bone metastasis or pain.

The following lists are provided for your reference but may not be all-inclusive. Refer to the Physician's Desk Reference for exclusion determination of a particular agent, or discuss with the study monitor or study clinician.

**Opioids:**

The following opioids are not permitted in this study:

| | |
|---|---|
| butorphanol* | meperidine* |
| nalbuphine* | pentazocine* |
| propoxyphene ** | |
| opioids in combination with non-opioids (such as acetaminophen or NSAIDs)*** | |

* Use not recommended by NCCN Guidelines[27];
** Withdrawn from some major markets due to safety concerns
*** Opioids in combination with acetaminophen may be permitted as standard of care analgesia from Week 8 onwards. Opioid-NSAID combinations are prohibited throughout the study until at least 16 weeks have passed since the last dose of study medication (Week 32 or Early Termination Visit 2).

Refer to 5.8.1.1.

**NSAIDs & COX-2 selective inhibitors:**

Use of NSAIDs and COX-2 selective inhibitors, both prescription or over-the-counter (OTC) is prohibited during the study until Week 32 except for occasional use.

Limited concomitant use of prescription or OTC NSAIDs may be allowed on an occasional basis for self-limiting conditions not related to cancer pain. However, they must not be taken within 48 hours of a study visit where efficacy assessments are being collected. NSAID use should not exceed a total of 36 days between Day 1 (Baseline) and Week 32 and the aggregate usage of NSAIDs during any one dosing interval (defined as the period of 8 weeks between 2 SC doses) should not exceed 10 days.

Management of NSAID use is described in Section 5.8.1.2.1. Washout period guidance is provided in Appendix 7.

Daily low dose aspirin (≤325 mg as per local prescribing practice) therapy for cardiovascular prophylaxis is permitted without restriction.

**Adjuvant analgesics:**

Use of concurrent adjuvant analgesics is permitted if started at least 30 days prior to the first day of the Baseline Assessment Period and maintained at a stable dose. These may include: single-agent acetaminophen (paracetamol), serotonin norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants, anticonvulsant medication, corticosteroids, or muscle relaxants. Treatment should not be initiated within 30 days of the start of the Baseline Assessment Period or during the study until at least Week 8.

**Other analgesics:**

The use of other analgesics (other than background opioids and permitted uses described in Section 5.8.2) is prohibited throughout the study beginning 48 hours (or 5 half-lives, whichever is longer) prior to the start of the Baseline Assessment Period and ending at Week 8.

Refer to Appendix 7: Half-Lives of NSAIDs and Other Analgesics, for a detailed washout schedule for analgesic medications. Sites must consult product labeling and conduct a taper according to the product instructions if a taper is required.

**Herbal, homeopathic, and naturopathic remedies:**

Herbal, homeopathic, and naturopathic remedies should not be initiated during the study; however, subjects who have taken a stable dose of these products for at least 30 days prior to start of the Baseline Assessment Period will be allowed to continue their regimen.

**Corticosteroids:**

Unless they were started at least 30 days prior to the first day of the Baseline Assessment Period and are maintained at a stable dose, oral or intramuscular corticosteroids used as concomitant analgesics are prohibited from the start of the Baseline Assessment Period through Week 8.

Oral or intramuscular corticosteroids used as concomitant analgesics starting less than 30 days prior to the Baseline Assessment Period must be washed out during the Screening Period for a period of at least 48 hours or 5 times the half-life of the particular corticosteroid (whichever is greater) before starting the Baseline Assessment Period. Intra-articular injection of corticosteroids to any major joint within 30 days prior to the Baseline Assessment Period through Week 32 is prohibited.

Limited use of oral, intramuscular or intravenous corticosteroids for non-analgesic purposes such as prophylaxis or treatment of chemotherapy-induced nausea and vomiting is permitted. Topical, inhaled and intranasal corticosteroids are permitted. Refer to Section 5.8.2.2 for details.

| Corticosteroid | Permitted | Prohibited |
|---|---|---|
| Oral or intramuscular corticosteroids used as concomitant analgesics | If started at least 30 days prior to the first day of the Baseline Assessment Period and maintained at a stable dose | If started within 30 days of the first day of the Baseline Assessment Period. Washout is required prior to the first day of the Baseline Assessment Period, and further use |

| | | |
|---|---|---|
| | | is prohibited until Week 8 |
| Oral, intramuscular or intravenous corticosteroids for non-analgesic purposes such as prophylaxis or treatment of chemotherapy-induced nausea and vomiting | Limited use is permitted | - |
| Intra-articular injection to any major joint | Allowable after Week 32 | Prohibited within 30 days prior to the Baseline Assessment Period through to Week 32 |
| Topical, inhaled and intranasal corticosteroids | Permitted throughout study | - |

| **Examples of Corticosteroids** | |
|---|---|
| **Generic** | **Brand** |
| betamethasone | Celestone, Soluspan |
| cortisone | |
| dexamethasone | Decadron, Dexacort, Turbinaire |
| fludrocortisone | Florinef |
| hydrocortisone | A-hydroCort, Cortef, Hydrocortone, Solu-Cortef |
| methylprednisolone | Medrol, Solu-Medrol |
| prednisolone | Orapred, Prelone |
| prednisone | Cortan, Deltasone, Medicorten |

**Chemotherapeutic, Radiopharmaceutical or Radiotherapy, Anti-Cancer Hormonal Treatments**

Concomitant chemotherapy is allowable, with some exceptions (see Section 5.8.2.3.), provided it was ongoing for at least 30 days before the first day of the Baseline Assessment Period. It is acceptable for the regimen to complete at any time after Randomization.

- A subject with chemotherapy-induced peripheral neuropathy can be enrolled provided the neuropathy has been stable over the 6 months prior to the start of the Baseline Assessment Period and the subject is no longer being treated with a chemotherapy agent associated with peripheral neuropathy (i.e. paclitaxel, docetaxel, oxaliplatin, cisplatin, vincristine, thalidomide and bortezomib).

- Chemotherapies associated with peripheral neuropathy (i.e. paclitaxel, docetaxel, oxaliplatin, cisplatin, vincristine, thalidomide and bortezomib) are not permitted from 30 days prior to the first day of the Baseline Assessment Period to Week 48 regardless of symptomatology.

Receipt of radiopharmaceutical treatment or radiotherapy for treatment of bone metastasis within 30 days of the first day of the Baseline Assessment Period and through to Week 8 is not permitted.

Concomitant hormonal anti-cancer treatment (eg, GnRH agonists or antagonists, anti-androgens or anti-estrogens) is allowable if treatment has been ongoing at stable dose for at least 30 days prior to the first day of the Baseline Assessment Period. Post Baseline, the concomitant hormonal anti-cancer treatment dose regimen should remain stable until at least Week 8.

If prior to Week 8, the subject's underlying cancer or bone metastasis progresses so as to require a new chemotherapy regimen, new concomitant bisphosphonates, new concomitant hormonal anti-cancer treatment, or initiation of radiotherapy to sites of bone metastasis, the subject should be withdrawn from study and entered in the Early Termination Follow-Up period (refer to Section 6.4).

Following the Week 8 visit, standard of care treatments may be initiated (refer to Section 5.8.2.3).

| **Criteria for Use of Chemotherapeutic, Radiopharmaceutical/ Radiotherapy or Hormonal Treatments*** | | |
|---|---|---|
| **Therapy** | **Permitted** | **Prohibited** |
| **Chemotherapy (see below for criteria regarding biologics)** | Allowable, with some exceptions (see Section 5.8.2.3.), if ongoing for at least 30 days before start of Baseline Assessment Period. | If a new chemotherapy regimen is required prior to Week 8, subject should be withdrawn and entered in the Early Termination Follow-Up period (refer to Section 6.4).<br><br>Chemotherapies associated with peripheral neuropathy (i.e. paclitaxel, docetaxel, oxaliplatin, cisplatin, vincristine, thalidomide and bortezomib) are not permitted from 30 days prior to the first day of the Baseline Assessment Period to Week 48 **regardless of symptomatology**. |
| **Radiopharmaceutical treatment or radiotherapy for bone metastasis** | Permitted if ≥30 days prior to first day of the Baseline Assessment Period. | Prohibited within 30 days of the first day of the Baseline Assessment Period through to Week 8.<br><br>If initiation of radiotherapy to sites of bone metastasis or new radiopharmaceutical regimen is required prior to Week 8, subject should be withdrawn and entered in the Early Termination Follow-Up period (refer to Section 6.4). |
| **Concomitant hormonal anti-cancer treatment (eg, GnRH agonists or antagonists, anti-androgens or anti-estrogens)** | Permitted if ongoing at stable dose for ≥30 days prior to first day of Baseline Assessment Period. | Post-Baseline, should remain stable until at least Week 8.<br><br>If initiation of new concomitant |

| | | |
|---|---|---|
| | | hormonal anti-cancer treatment is required prior to Week 8, subject should be withdrawn and entered in the Early Termination Follow-Up period (refer to Section 6.4). |

*Following the Week 8 visit, standard of care treatments may be initiated (refer to Section 5.8.2.3).

**Biologics**

Monoclonal antibodies used for the treatment of underlying cancer or bone are generally permitted if ongoing at stable dose regimen at least 30 days prior to the first day of the Baseline Assessment Period (see Section 5.8.2.3.) and not meeting other exclusionary criteria. Standard of care treatments may be initiated following the Week 8 visit, if required.

Monoclonal antibody therapies associated with clinically significant peripheral or autonomic neuropathy or joint-related adverse effects or those based on chimeric or murine antibodies are prohibited within 90 days of the start of the Baseline Assessment Period and during the study until Week 32.

Examples of permitted and prohibited monoclonal antibody therapies are provided in the following list for your reference but may not be all inclusive. Therapies which are not specifically listed should be discussed with the study clinician on a case-by-case basis.

Small molecule inhibitors used in the treatment of underlying cancer or bone metastasis are permitted (except for bortezomib) if at a stable dose regimen at least 30 days prior to the first day of the Baseline Assessment Period.

Cell/gene therapies, investigational therapies, or TNF-α inhibitors are generally prohibited and must not be taken within 90 days prior to start of the Baseline Assessment Period or during the study until Week 32.

| **Criteria for Use & Examples of Biologics** | | |
|---|---|---|
| **Biologic** | **Permitted**<br>**Generic (Brand)** | **Prohibited**<br>**Generic (Brand)** |
| **Monoclonal antibodies used in the treatment of underlying cancer or bone metastasis*** | Permitted if not meeting exclusion criteria and at a stable dose regimen at least 30 days prior to the first day of the Baseline Assessment Period.<br><br>Eg,<br>Bevacizumab (Avastin)<br>Trastuzumab (Herceptin)<br>Panitumumab (Vectibix)<br>Denosumab (Prolia, Xgeva)<br>Nivolumab (Opdivo) | Prohibited if associated with significant neurologic or musculoskeletal adverse effects or those based on chimeric or murine antibodies are prohibited from within 90 days of the start of the Baseline Assessment Period and for the duration of the study until Week 32.<br><br>Eg,<br>Cetuximab (Erbitux) |

| | | |
|---|---|---|
| | Pembrolizumab (Keytruda)<br>Ramucirumab (Cyramza) | **Ado**-trastuzumab emtansine (Kadcyla)<br><br>Chemotherapies associated with peripheral neuropathy are not permitted from 30 days prior to the first day of the Baseline Assessment Period to Week 48 regardless of symptomatology. |
| **Small molecule inhibitors used in the treatment of underlying cancer or bone metastasis** | Permitted if at a stable dose regimen at least 30 days prior to the first day of the Baseline Assessment Period, except for bortezomib.<br><br>Eg,<br>Erlotinib hydrochloride (Tarceva)<br>Sunitinib (Sutent)<br>Lapatinib (Tykerb) | Prohibited if at unstable dose regimen or initiated within 30 days prior to the start of the Baseline Assessment Period.<br><br>Bortezomib is not permitted from 30 days prior to the first day of the Baseline Assessment Period to Week 48. |
| **TNFα Inhibitors** | None permitted until Week 32 | Prohibited within 90 days prior to start of the Baseline Assessment Period and during the study until Week 32.<br><br>Eg,<br>Adalimumab (Humira)<br>Etanercept (Enbrel)<br>Infliximab (Remicade) |
| **Blood products** | Blood transfusion<br>Eg, whole blood, platelets<br><br>Leukocyte growth factors<br>Eg, Filgrastim (Neupogen)<br><br>Erythropoietin-stimulating agents<br>Eg, Epoetin alfa (Epogen) | - |
| **Cell/gene therapies** | None permitted | Prohibited within 90 days prior to start of the Baseline Assessment Period and during the study. |

*Monoclonal antibody therapies which are not specifically listed as permitted or prohibited should be reviewed with the study clinician prior to enrollment.

## Vaccines:

Inactivated viral or bacterial vaccines are permitted. Eg, Influenza (Fluzone, Agriflu), Pneumococcus (Pneumovax), Tetanus, [reduced] Diphtheria (Td).

Use of live attenuated vaccines (with the exception of Flumist® Influenza Virus Vaccine Live, Intranasal or other inhaled live attenuated influenza vaccines) is prohibited within 90 days of the start of the Baseline Assessment Period and during the study.

| **Prohibited Live Attenuated Vaccines** | |
|---|---|
| **Generic** | **Brand** |
| BCG (for tuberculosis) | Not available in the US |
| Herpes zoster vaccine | Zostavax |
| Measles | Attenuvax |
| Measles, Mumps, and Rubella (MMR) | MMR |
| Mumps | Mumpsvax |
| Oral poliovirus vaccine, oral | OPV (no longer available in the US) |
| Rotavirus, oral | RotaTeq |
| Rubella | Meruvax II |
| Smallpox | Dryvax (Not commercially available in the US) |
| Typhoid, oral | Vivotif Berna |
| Varicella zoster | Varivax |
| Yellow fever | YF-VAX |

## Appendix 9. Daily/Weekly Pain IRT Assessments

### Index Bone Metastasis Cancer Pain Site Assessment

Average pain example question for the index bone metastasis cancer pain site:

Select the number that best describes your average pain in your <*insert index site of bone metastasis pain*> in the past 24 hours:

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| No Pain | | | | | | | | | | Worst Possible Pain |

Worst pain example question for the index bone metastasis cancer pain site:

Select the number that best describes your worst pain in your <*insert index site of bone metastasis pain*> in the past 24 hours:

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| No Pain | | | | | | | | | | Worst Possible Pain |

### Non-index site(s) of Cancer Pain Assessment

Average pain example question for the non-index site(s) of cancer pain:

Select the number that best describes your average pain in your <*insert non-index site of cancer pain*> in the past 24 hours:

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| No Pain | | | | | | | | | | Worst Possible Pain |

Worst pain example question for the non-index site(s) of cancer pain:

Select the number that best describes your worst pain in your <*insert non-index site of bone metastasis pain*> in the past 24 hours:

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| No Pain | | | | | | | | | | Worst Possible Pain |

**Joint Pain Assessments**

Example question for major joints (each shoulder, hip and knee and any other major joint for which a radiograph is obtained):

Select the number that best describes your average pain in your < *insert name and laterality of major joint*> in the past 24 hours:

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| No Pain | | | | | | | | | | Worst Possible Pain |

CCI [redacted]

## Appendix 11. Opioid-Related Symptom Distress Scale

The subject will complete the following table detailing his/her experience with respect to the study medication taken for pain.

**We have listed 10 symptoms below. Read each one carefully. If you have had the symptom during the past 24 hours, let us know how OFTEN you had it, how SEVERE it was usually and how much it DISTRESSED OR BOTHERED you by placing an "X" in the appropriate box. If you DID NOT HAVE the symptom, please place an "X" in the box marked "Did not have".**

**For the symptom "retching/vomiting" below, you will indicate the actual number of episodes you experienced.**

During the last 24 hours, did you have any of the following?

| Symptom | Did not have | (If yes), how often did you have it? | | | | (If yes), how severe was it usually? | | | | (If yes), how much did it distress or bother you? | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Rarely | Occasionally | Frequently | Almost Constantly | Slight | Moderate | Severe | Very Severe | Not at all | A little bit | Somewhat | Quite a Bit | Very Much |
| Fatigue | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Drowsiness | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Inability to concentrate | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Nausea | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Dizziness | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Constipation | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Itching | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Difficulty with urination | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Confusion | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Retching/vomiting | ☐ | __ __ # of episodes | | | | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

## Appendix 12. Patient Global Assessment of Cancer Pain

Subjects will answer the following question:

**Considering all the ways your cancer pain affects you, how are you doing today?**

Subjects will rate their condition using the following scale:

| Grade | Description |
|---|---|
| 1 – Very Good | Asymptomatic and no limitation of normal activities |
| 2 – Good | Mild symptoms and no limitation of normal activities |
| 3 – Fair | Moderate symptoms and limitation of some normal activities |
| 4 – Poor | Severe symptoms and inability to carry out most normal activities |
| 5 – Very Poor | Very severe symptoms which are intolerable and inability to carry out all normal activities |

CCI

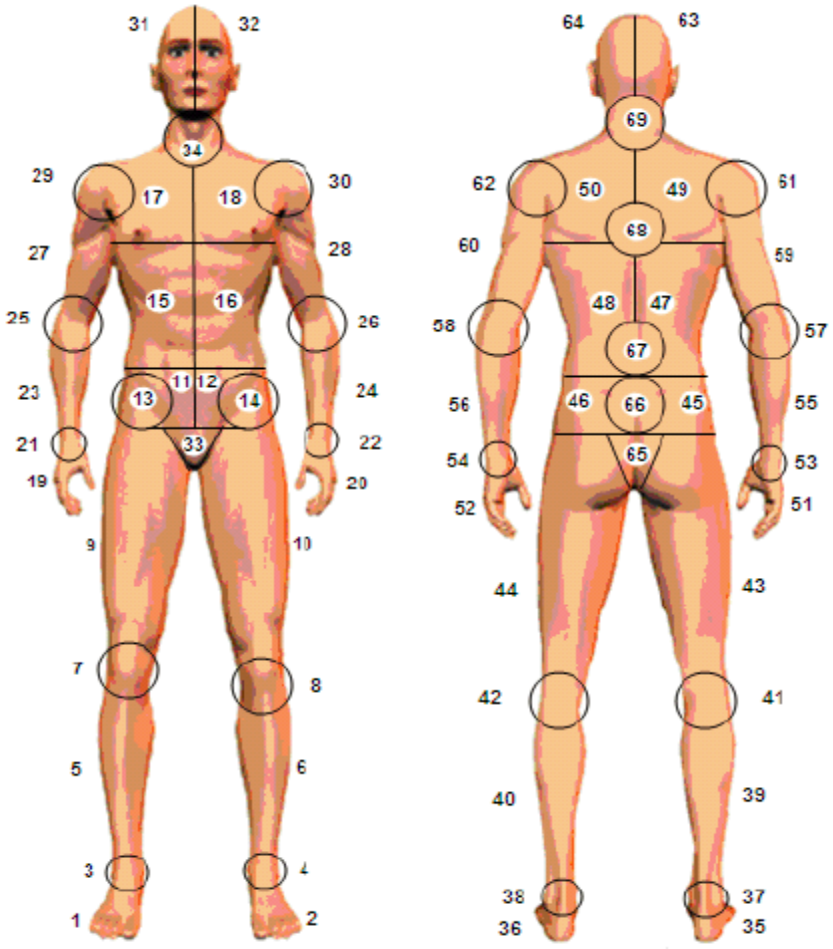

CCI

CCI

## Appendix 15. Example for Reporting Daily/Weekly NRS Pain Scores

As an example, assume that a subject has a painful bone metastasis (7 out of 10 average NRS rating) in the lower lumbar region. In addition, the subject has a painful visceral metastasis in the right abdomen (4 out of 10 average NRS). Finally, the subject has a mild, stable painful chemotherapy-induced peripheral neuropathy in both feet (3 out of 10 average NRS).

The subject may be shown a diagram on the IRT such as the one shown below to enable the subject to note the location of painful sites. In this example, assume that the subject is able to select painful sites according to the number shown on the diagram.




At Screening, the subject will be asked to select the most painful site of bone metastasis pain, (which in the example diagram below would be site # 67) and to provide average and worst pain ratings for this site. Once confirmed by the investigator, this will be the index site of bone metastasis cancer pain.

The subject will be asked via the IRT whether he or she is experiencing cancer pain in site(s) other than the index site of bone metastasis cancer pain. If yes, the subject will be asked to specify up to 2 additional painful sites. In this case, the subject will select site #1, (although

alternatively, site #2 could have been selected since the pain was equal in each foot), and site #15 as additional sites of pain and will provide average and worst pain ratings for each site. Once confirmed by the investigator, these sites will be the non-index sites of cancer pain.

At Screening the investigator will confirm that the site identified by the subject as the most painful site corresponds to a site of bone metastasis (ie, the investigator will confirm the index bone metastasis cancer pain site). In addition, for other non-index sites of cancer pain selected by the subject, the investigator will confirm that pain at each site is due to cancer or cancer treatment (eg, chemotherapy induced peripheral neuropathy) and will indicate whether in his/her judgment the cancer pain for each site is somatic, neuropathic or visceral in nature.

In this example at Screening, the investigator would confirm that the most painful site (site #67) is the index bone metastasis cancer pain site and would confirm that sites #1 and #15 are non-index cancer pain sites. The investigator would indicate site #1 represents neuropathic pain, and site #15 represents visceral pain.

After Screening, the IRT will be programmed to display either the index bone metastasis cancer pain site (for daily assessments) or both the index site and non-index sites of cancer pain (for weekly assessments) selected at Screening so the subject can provide pain ratings for these sites during the study.

## Appendix 16. Substudy for Subjects Undergoing Total Joint Replacement of the Hip, Knee or Shoulder

### SUBSTUDY SUMMARY

Measures to better characterize the joint safety issue identified in 2010 have been developed and agreed with FDA. The post-arthroplasty data collected within this substudy, when aggregated with similar data from other tanezumab clinical studies, fulfills one component of the agreed risk characterization measures and is an attempt to address the potential concern that subjects treated with tanezumab have a different post-surgical outcome than those not treated with tanezumab. The total joint replacement data from completed tanezumab studies does not suggest a different post-surgical outcome in tanezumab treated subjects however those data were gathered retrospectively. The types of endpoints to be assessed in this prospective substudy and the duration of this substudy have been agreed to with the FDA. Every effort will be made to enroll all A4091061 subjects who undergo a qualifying total joint replacement into this substudy however it is acknowledged that to a certain extent the population enrolled in this substudy will be 'self-selected' and thus there may be subjects with a qualifying total joint replacement who choose not to enter the substudy.

This substudy is a long-term observational study of subjects from tanezumab Study A4091061 (regardless of treatment group) who undergo a total knee, hip or shoulder replacement during participation in the study (Treatment Period and Safety Follow-Up period). If while the subject is participating in this substudy, the subject undergoes an additional total joint replacement surgery or the site becomes aware that an additional total joint replacement surgery has been scheduled for the subject, the subject will be requested to provide information on the additional total joint replacement surgery as well. Finally, any subject with a qualifying total joint replacement after the last subject completes the treatment period in study A4091061 may be followed in study A4091064 which is a separate study with a design similar to this substudy.

This substudy is designed with a total duration of subject follow-up of 24 weeks after the total joint replacement surgery. There will be two methods of data collection utilized in this substudy: interview by site staff via the telephone and interactive web response system (IWRS) accessed by desktop, laptop or tablet computer (or paper if the subject has no access to the internet via a desktop, laptop or tablet computer). Following the surgery, the subject will be contacted monthly via telephone by study site personnel to ascertain whether the subject has experienced any adverse events and to record any concomitant analgesic medications the subject is taking as well as the reason for the medication use. An assessment of the subject's overall satisfaction with their total joint replacement (IWRS), average pain in the replaced joint (IWRS), the subject's level of function and activity in the replaced joint (IWRS) and physical rehabilitation activities (telephone interview) will be made at Weeks 4, 12 and 24. At Weeks 12 and 24, subjects will be queried during the telephone interview as to whether any additional or corrective procedures related to the total joint replacement are planned.

All events of total knee, hip or shoulder replacement will be reviewed by the Joint Safety Adjudication Committee (Adjudication Committee) established for the tanezumab clinical

program. This Committee will adjudicate in an independent and blinded fashion if the event is primary osteonecrosis, worsening OA (further sub-divided into rapidly progressive OA (RPOA) type 1 or type 2, normal progression of OA or not enough information to distinguish between RPOA and normal progression of OA), subchondral insufficiency fracture, pathologic fracture, other (with diagnosis specified) or not enough information to specify a diagnosis. Prior to the Adjudication Committee's review of a given event, Committee members will be provided with blinded, available source documentation of progress reports from the investigator, orthopedic consult reports, operative reports, the pathology report from the Central Laboratory, radiology reports, Dual Energy X-ray Absorptiometry (DEXA) reports, x-ray images and MRI for review. In addition, blinded summaries of the following data from Study A4091061 will be provided to the Committee members for review for each event undergoing adjudication: demographic and Baseline characteristics, medical history and concomitant medications, study medication administration, non-drug treatments, subject disposition, efficacy data, adverse event information, CCI and a serious adverse event narrative (if applicable).

Subjects, investigators, study coordinators, clinical site staff, orthopedic surgeons, and clinical research associates (CRAs) and staff directly involved with this substudy at Pfizer and its designees will be blinded to treatment assignment in Study A4091061.

The number of subjects who will enroll in this substudy is unknown but is estimated to be less than 25 subjects. Also unknown is the distribution of subjects across treatment groups (ie, the treatment given in Study A4091061). Therefore, it is predicted that there will be insufficient statistical power to perform statistical inferential analyses. All analyses will be descriptive in nature. The data collected in this substudy will be combined with similar data collected in other tanezumab studies for further analysis. These aggregate analyses will be reported separately.

## Table 5. Schedule of Activities

| Substudy Activities | | | Post-Surgery | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Baseline[a] | Day 1 | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 24/ET |
| | Last visit in Study A4091061[b] or when notified of TJR surgery | Day of Surgery (+10 days) | Day 29 (±5 days) | Day 57 (±5 days) | Day 85 (±5 days) | Day 113 (±5 days) | Days 141 (±5 days) | Day 169 (±5 days) |
| **Pre-surgery Activities** | | | | | | | | |
| Informed Consent | X | | | | | | | |
| Inclusion Criteria Review | X | | | | | | | |
| Record ongoing adverse events and concomitant analgesic medication | X | | | | | | | |
| Train subject in the use of the ePRO system (IWRS) if applicable [c] | X | | | | | | | |
| Assessment of Pain in Joint to be Replaced (11-point NRS) [d] | X | | | | | | | |
| Assessment of Functional Status (WOMAC [total hip or knee replacement candidates] or SPADI [total shoulder replacement candidates ]) [d] | X | | | | | | | |
| Provide surgery-related documents (Surgeon's Assessment of Procedural Difficulty and Pathology Specimen Collection/Shipment Guidelines) to Surgeon | X | | | | | | | |
| **Surgery - related Activities** | | | | | | | | |
| Obtain Surgeon's Assessment of Procedural Difficulty | | X | | | | | | |
| Confirm pathology specimens were shipped according to instructions | | X | | | | | | |
| Ensure required source documents are provided to Endpoint Management Team | | → | X | | | | | |
| **Post-Surgery Subject Follow-up Activities** | | | | | | | | |
| **Telephone-based Assessments** | | | | | | | | |
| Adverse events | | | X | X | X | X | X | X |
| Concomitant analgesic medication use | | | X | X | X | X | X | X |

| Substudy Activities | | | Post-Surgery | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Baseline[a] | Day 1 | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 24/ET |
| | Last visit in Study A4091061[b] or when notified of TJR surgery | Day of Surgery (+10 days) | Day 29 (±5 days) | Day 57 (±5 days) | Day 85 (±5 days) | Day 113 (±5 days) | Days 141 (±5 days) | Day 169 (±5 days) |
| Participation in physical rehabilitation activities related to the replaced joint | | | X | | X | | | X |
| Additional or corrective procedures related to the replaced joint | | | | | X | | | X |
| Remind subjects not utilizing the IWRS to return paper-based assessments to the site within 5 days | | | X | | X | | | X |
| Remind subjects of contraceptive requirements (if applicable) [e] | | | X | X | X | X | | |
| **Web-based Assessments** [f] | | | | | | | | |
| Subject's overall satisfaction with joint replacement surgery (SAPS) | | | X | | X | | | X |
| Pain in replaced joint (11-point NRS) | | | X | | X | | | X |
| Functional status (WOMAC [total hip and knee replacement subjects] or SPADI [total shoulder replacement subjects] [g] | | | X | | X | | | X |

a. Baseline activities must be conducted at the site.
b. Last visit in Study A4091061 can be either the end of study visit or early termination visit.
c. Training in the use of the ePRO system (IWRS) is appropriate for subjects who will have access to the internet via a desktop, laptop or tablet computer for the duration of the study.
d. To be collected via the Interactive Web Response System (IWRS). If the subject will not have access to the IWRS via a desktop, laptop or tablet computer for the duration of the study, paper versions of the assessment should be completed by the subject with subsequent entry into the IWRS by site staff. Note: the WOMAC and SPADI should be completed in their entirety.
e. Female subjects of child-bearing potential should be reminded of contraception requirements if less than 112 days (16 weeks) have elapsed since the last dose of subcutaneous study medication in Study A4091061.
f. If the subject does not have access to the IWRS via a desktop, laptop or tablet computer for the duration of the study, paper versions of the assessments should be completed by the subject. Completed paper assessments should be returned to the clinical site as soon as possible, but no later than 5 days, after completion of the assessment. Site staff will enter the subject reported outcomes into the IWRS upon receipt of the completed assessment.
g. The WOMAC and SPADI should be completed in their entirety.

## 101. SUBSTUDY INTRODUCTION

Measures to better characterize the joint safety issue identified in 2010 have been developed and agreed with FDA. The post-arthroplasty data collected within this substudy, when aggregated with similar data from other tanezumab clinical studies, fulfills one component of the agreed risk characterization measures and is an attempt to address the potential concern that subjects treated with tanezumab have a different post-surgical outcome than those not treated with tanezumab. The total joint replacement data from completed tanezumab studies does not suggest a different post-surgical outcome in tanezumab treated subjects however those data were gathered retrospectively from previous studies. The types of endpoints to be assessed in this prospective substudy and the duration of the substudy have been agreed to with the FDA. Every effort will be made to enroll all Study A4091061 subjects who undergo a qualifying total joint replacement into this substudy however it is acknowledged that to a certain extent the population enrolled in this substudy will be 'self-selected' and thus there may be subjects with a qualifying total joint replacement who choose not to enter the substudy.

Every effort will be made to comply with all protocol required procedures however it is acknowledged that some protocol requirements could prove operationally difficult to complete. For example investigators may be notified of a subject's total joint replacement after the surgery and therefore baseline data are not available; the surgeon performing the total joint replacement surgery may be unable or unwilling to cooperate with requests to complete the Surgeon's Assessment of Procedural Difficulty; or local or national regulations may preclude provision of the pathology specimen. Any of these potential operational difficulties should not preclude a consenting subject from participating in the A4091061 substudy. Every effort should be made to obtain any protocol-specified information that the subject and surgeon are able to provide.

### 101.1. Rationale for Selected Patient Reported Outcomes

Subject-based measures of health-related quality of life have increasingly been used by the orthopedic research community as a means to define a successful intervention.[1] Subject reported outcomes typically assessed post-arthroplasty include overall satisfaction with the joint replacement, pain and function.

The Self-Administered Patient Satisfaction Scale (SAPS) will be utilized to assess subject satisfaction with the joint replacement in this substudy. The SAPS is a multidimensional, disease specific measure that evaluates subject satisfaction with the outcome of hip or knee arthroplasty and was designed to be used in conjunction with other clinical measures and functional health status instruments to evaluate the results of hip and knee arthroplasty. The validity and reliability of the scale has been demonstrated.[2] The scale consists of four items focusing on satisfaction with the extent of pain relief, improvement in ability to perform home or yard work, ability to perform recreational activities and overall satisfaction with joint replacement.

Average pain in the joint to be replaced (pre-surgery) and the replaced joint (post-surgery) will be assessed with an 11-point Numeric Rating Scale (NRS) ranging from zero (no pain) to 10 (worst possible pain). The validity and reliability of the scale has been demonstrated.[3]

The functional measures chosen for this substudy were those which have been shown to be valid, reliable and sensitive and in addition were region-specific and easy to administer. Subjects undergoing total knee or hip replacement will be asked to complete the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) with the knee or hip that was replaced serving as the "index joint". Subjects undergoing total shoulder replacement will be asked to complete the Shoulder Pain and Disability Index (SPADI).

The WOMAC is a self-administered condition-specific instrument which assesses pain, disability and joint stiffness in knee and hip osteoarthritis. It is a valid, reliable and responsive measure of outcome in subjects with arthritis and has been used extensively.[4,5,6]

The SPADI is a self-administered questionnaire that was developed to measure the pain and disability associated with shoulder pathology in people with shoulder pain of musculoskeletal, neurogenic or undetermined origin. The psychometric properties of the SPADI have been shown to be acceptable for research use and the SPADI has been recommended to assess outcomes in subjects undergoing shoulder arthroplasty.[7,8] The instrument consists of two dimensions (pain and function). The pain dimension consists of five questions regarding the severity of an individual's pain. Functional activities are assessed with eight questions designed to measure the degree of difficulty an individual has with various activities of daily living that require upper extremity use.

### 101.2. Interactive Web Response System

To avoid a social desirability bias in the subject reported outcomes, an Interactive Web Response System (IWRS) will be utilized in this substudy. Contingency plans will be in place to address system and/or connectivity issues with the IWRS.

However, eligibility for this substudy does not require access to the internet via a desktop, laptop or tablet computer so, for those subjects without access to the internet via a desktop, laptop or tablet computer, paper versions of the assessments will be utilized. Though not optimal, the use of two methods to collect subject reported outcomes will maximize the ability to capture information from all subjects who undergo a total knee, hip, or shoulder replacement surgery while participating in Study A4091061. Additional considerations which mitigate the concerns about using two methods to collect subject reported outcomes in the same substudy include that this substudy has not been formally powered and all analyses will be descriptive rather than inferential.

## 102. SUBSTUDY OBJECTIVE AND ENDPOINTS

### 102.1. Objective

To describe the post-operative outcome of subjects who underwent a total knee, hip, or shoulder replacement while participating in Study A4091061 (Treatment Period and Safety Follow-Up period).

### 102.2. Endpoints

The following endpoints will be assessed in this substudy:

- Surgeon's Assessment of Procedural Difficulty: number and percentage of surgeries assessed as uneventful, minor complications or major complications.

- Subjects' overall satisfaction with surgery as assessed by the Self-Administered Patient Satisfaction (SAPS) Scale: number and percentage of subjects satisfied versus unsatisfied with their total joint replacement at Week 24.

- Number and percentage of subjects with a post-surgical complication(s) up to Week 24 (derived from reported adverse events).

- Number and percentage of subjects with additional or corrective procedures related to their total joint replacement up to Week 24.

- Number and percentage of subjects participating in physical rehabilitation activities related to the replaced joint up to Week 24.

- Change from Baseline to Week 24 in average pain in the replaced joint.

- Change from Baseline to Week 24 in WOMAC Pain, Stiffness and Physical Function subscales in the replaced joint (subjects undergoing total hip or knee replacement surgery only).

- Change from Baseline to Week 24 in the SPADI in the replaced shoulder (subjects undergoing total shoulder replacement surgery only).

- Concomitant analgesic medication use.

## 103. SUBSTUDY STUDY DESIGN

This substudy is a long-term observational study of subjects from tanezumab Study A4091061 (regardless of treatment group) who undergo a total knee, hip or shoulder replacement during participation in the study (Treatment Period or Safety Follow-Up period). If while the subject is participating in this substudy, the subject undergoes an additional total joint replacement surgery or the site becomes aware that an additional total joint replacement surgery has been scheduled for the subject, the subject will be requested to provide information on the additional total joint replacement surgery as well. Finally, any subject with a qualifying total joint replacement after the last subject completes the treatment period in study A4091061 may be followed in study A4091064 which is a separate study with a design similar to this substudy.

This substudy is designed with a total duration of subject follow-up of 24 weeks after the total joint replacement surgery. There will be two methods of data collection utilized in this substudy: interview by site staff via the telephone and IWRS accessed by desktop, laptop or tablet computer (or paper if the subject has no access to the internet via a desktop, laptop or tablet computer). Following the surgery, the subject will be contacted monthly via telephone by study site personnel to ascertain whether the subject has experienced any adverse events and to record any concomitant analgesic medications the subject is taking as well as the reason for the medication use. An assessment of the subject's overall satisfaction with their

total joint replacement (IWRS), average pain in the replaced joint (IWRS), the subject's level of function and activity in the replaced joint (IWRS) and physical rehabilitation activities (telephone interview) will be made at Weeks 4, 12 and 24. At Weeks 12 and 24, subjects will be queried during the telephone interview as to whether any additional or corrective procedures related to the total joint replacement are planned.

Any subject who expresses a desire to leave this substudy before 24 weeks of follow-up have been completed should be asked to complete all assessments scheduled for Week 24.

All events of total knee, hip or shoulder joint replacement will be reviewed by the Joint Safety Adjudication Committee (Adjudication Committee) established for the tanezumab clinical program. This Committee will adjudicate in an independent and blinded fashion if the event is primary osteonecrosis, worsening OA (further sub-divided into rapidly progressive OA (RPOA) type 1 or type 2, normal progression of OA or not enough information to distinguish between RPOA and normal progression of OA), subchondral insufficiency fracture, pathologic fracture, other (with diagnosis specified) or not enough information to specify a diagnosis. Prior to the Adjudication Committee's review of a given event, Committee members will be provided with blinded, available source documentation of progress reports from the investigator, orthopedic consult reports, operative reports, the pathology report from the Central Laboratory, radiology reports, DEXA reports, x-ray images and MRI images for review. Sites will be requested to submit required source documentation to the Endpoint Management Team as soon as possible, and ideally within 29 ± 5 days, after the total joint replacement surgery (ie, by the time the Week 4 visit occurs provided the source documentation has been completed). In addition, blinded summaries of the following data from Study A4091061 will be provided to the Committee members for review for each event undergoing adjudication: demographic and Baseline characteristics, medical history and concomitant medications, study medication administration, non-drug treatments, subject disposition, efficacy data, adverse event information, CCI CCI and a serious adverse event narrative (if applicable).

The Adjudication Committee, in coordination with the E-DMC, is responsible for ongoing analysis of these outcomes and for informing the sponsor of recommendations made.

Subjects, investigators, study coordinators, clinical site staff, orthopedic surgeons, clinical research associates (CRAs) and staff directly involved with this substudy at Pfizer and its designee will be blinded to treatment assignment in Study A4091061. The data collected in this substudy will be combined with similar data collected in other tanezumab studies for analysis. Data analyses will be reported separately.

## 104. SUBSTUDY SUBJECT SELECTION

This substudy can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom the substudy is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this substudy is suitable for a particular subject.

### 104.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team (ie, the investigator or a sub-investigator) before subjects are included in this substudy.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the substudy:

1. Evidence of a personally signed and dated informed consent document indicating the subject (or a legal representative) has been informed of all pertinent aspects of the substudy.

2. Subject has been randomized and treated with SC study medication in tanezumab Study A4091061 and has completed the study or has been withdrawn from the study.

3. Actual or planned total knee, hip or shoulder replacement surgery during Study A4091061. Note: additional procedures in a subject undergoing total joint replacement surgery (eg, revision of a previously replaced joint in addition to a new total joint replacement) will be allowed, but subjects undergoing solely sub-total arthroplastic procedures (eg, hemi-arthroplasty) will not be eligible.

4. Subject is willing and able to comply with scheduled visits and other substudy procedures.

### 104.2. Life Style Guidelines

All female subjects who are of childbearing potential and are sexually active and at risk for pregnancy, and **who withdraw from Study A4091061 less than 16 weeks after the last dose of subcutaneous investigational product** must agree to use one (1) method of highly effective contraception consistently and correctly **until 112 days (16 weeks) after the last dose of subcutaneous investigational product**. The investigator or his/or her designee, in consultation with the subject, will confirm the subject has selected the most appropriate form of contraception for the individual subject from the permitted list of contraception methods (see below), and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for correct use of the selected method of contraception. The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the schedule of activities and document such conversation in the subject's chart. In addition, the Investigator or his/or her designee will instruct the subject to call immediately if the selected birth control methods are discontinued or if pregnancy is known or suspected in the subject.Refer to Section 4.4 of the protocol for guidance on appropriate methods of contraception.

There are no contraception requirements for sexually active female subjects of childbearing potential who withdraw from Study A4091061 more than 16 weeks after the last dose of subcutaneous investigational product.

### 104.3. Sponsor Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for this substudy is documented in the study contact list located in the Study Manual (refer to Section 4.5 of the A4091061 protocol).

## 105. SUBSTUDY STUDY TREATMENTS

This is an observational study of subjects who were randomized and treated in tanezumab Study A4091061 and who subsequently underwent a total knee, hip or shoulder replacement during the Treatment or Safety Follow-Up period. There are no study medications in this observational study.

Subjects, investigators, study coordinators, clinical site staff, orthopedic surgeons, clinical research associates (CRAs) and staff directly involved with this substudy at Pfizer and its designees will be blinded to treatment assignment in Study A4091061.

### 105.1. Concomitant Medication(s)

No medications are specifically prohibited in this observational substudy.

Subjects who enter into this substudy <16 weeks after their last dose of subcutaneous study medication in Study A4091061 will be advised to avoid chronic NSAID use or intra-articular corticosteroids, until at least 16 weeks has elapsed, if possible.

Subjects will be instructed to keep a record of concomitant analgesic medication usage (including dose, dosing regimen and reason for use). This information will be recorded on the appropriate concomitant medication case report form (CRF) during the monthly telephone interviews.

## 106. SUBSTUDY STUDY PROCEDURES

Study visit windows are +10 days for activities related to the total joint replacement surgery and ±5 days for activities performed on Weeks 4, 8, 12, 16, 20 and 24. Site staff should make every effort to contact the subject within the defined visit window for Weeks 4, 8, 12, 16, 20 and 24 however, data obtained outside of the visit window while a deviation, should still be recorded. In the event that the activities related to a visit are performed within the extremes of the visit windows, following study visits and associated activities should be scheduled with reference to the total joint replacement surgery date. Subject scheduling issues should be brought to the attention of study management for resolution.

The investigator must make sure that delegations of responsibility to site staff for administering the IWRS or entering data into the IWRS are specifically documented using the appropriate forms and are based on documented evidence of adequate training in administration and use of the IWRS. The investigator (or other site staff specifically delegated by the investigator) is responsible for regular monitoring of the compliance of the subjects with the required data entry by means of reports in the IWRS. The IWRS will also be programmed to notify designated site staff when data has not been recorded within the requested timeframe. Regardless of how the investigator delegates responsibility for administering the IWRS or entering data into the IWRS, the investigator remains responsible

for providing adequate supervision and oversight of the investigator's colleagues, employees and any third parties as per FDA regulations and guidelines and Good Clinical Practice.

### 106.1. Baseline Visit (Last Visit in Study A4091061 or when Notified of TJR Surgery)

Baseline information for this substudy should be obtained as close as possible to, and prior to, the total joint replacement surgery. The Baseline Visit may coincide with the last visit in Study A4091061 (End of Study or Early Termination Visit) or occur when the site is notified of a planned total joint replacement surgery. Baseline Visit activities must be conducted at the clinical site.

If a planned surgery is postponed such that more than 30 days has elapsed since the baseline pain and function assessments for the substudy were recorded, if possible, repeat assessments of pain and function should be recorded.

Subjects should be queried about their access to the internet via a desktop, laptop or tablet computer so as to determine the appropriate format for the subject reported outcomes of pain in the joint to be (or post-surgery, that has been) replaced, functional status and, post-surgery, satisfaction with surgery.

Subjects with access to the internet via a desktop, laptop or tablet computer should be trained in the use of the IWRS and in their responsibilities for data entry in compliance with this substudy protocol. IWRS technical support (Help Desk) will be available to the subject for the duration of the study. Beginning with the Baseline Visit, subjects with access to the internet via a desktop, laptop or tablet computer should complete the aforementioned assessments via the IWRS. In the event of internet connectivity issues at the Baseline Visit, paper versions of the assessments should be completed.

Only subjects without access to the internet via a desktop, laptop or tablet computer during this substudy should complete the aforementioned assessments on paper for the duration of the substudy. Simple preference for the use of paper is not sufficient to allow its use by the subject who has access to the internet via a desktop, laptop or tablet computer during this substudy.

Except in unusual circumstances, subjects should not switch between paper-based and web-based completion of the subject reported outcome measures.

Thorough instruction should be provided for completion of self-administered scales (subject reported outcomes) however, no coaching or other interpretative assistance should be given to the subject during the completion of the questionnaires.

Telephone contact information should also be confirmed at the Baseline Visit.

#### 106.1.1. Activities at the Baseline Visit:

- Informed consent.
- Review of inclusion criteria.

- Record ongoing adverse events and concomitant analgesic medications.
- Assessment of pain in the joint to be replaced (11-point NRS).
- Assessment of functional status in the joint to be replaced (WOMAC for subjects undergoing total knee or hip replacement or SPADI for subjects undergoing total shoulder replacement). NOTE: the WOMAC and SPADI should be completed in their entirety.
- Subjects without access to the internet via a desktop, laptop or tablet computer should be provided with paper copies of the subject reported outcomes assessments. Subjects should be instructed on the timing of assessments and the need to return the assessments to the site as soon as possible, but no later than 5 days, after completion of the assessment.
- Study site staff must contact the subject's orthopedic surgeon to discuss the completion of the required forms and specimen collection and handling. The surgeon will be provided with the surgery related documents (Surgeon's Assessment of Procedural Difficulty and instructions for the shipment of pathology specimens). Where possible study site staff should contact the surgeon to discuss required forms and specimen collection and handling.
- If less than 112 days (16 weeks) have elapsed since the last dose of subcutaneous study medication in Study A4091061, female subjects of child-bearing potential should be reminded of contraceptive requirements.

**106.2. Day of Surgery (Day 1 + 10 days)**

During this interval, sites should ensure receipt of a completed Surgeon's Assessment of Procedural Difficulty and confirm that pathology specimens were shipped according to instructions. Required source document collection (eg, operative report and discharge summary) should begin in this interval.

Sites will be requested to submit required source documentation to the Endpoint Management Team as soon as possible, and ideally within 29 ± 5 days, after the total joint replacement surgery (ie, by the time the Week 4 visit occurs provided the source documentation has been completed).

**106.3. Week 4 (Day 29 ± 5 days)**

Site staff should contact the subject via telephone to:

- Query for adverse events.
- Query for concomitant analgesic medication use (record dose, dosing regimen and reason for use).

- Query about physical rehabilitation activities subsequent to the total joint replacement surgery.

During the telephone call, site staff should instruct the subject to complete the following assessments either via the IWRS or via paper, as established at the Baseline Visit:

- Pain in Replaced Joint (11-point NRS).
- Functional status (WOMAC for subjects with a total knee or hip replacement or SPADI for subjects with a total shoulder replacement); NOTE: the WOMAC and SPADI should be completed in their entirety.
- Overall satisfaction with joint replacement surgery measured by the Self-Administered Patient Satisfaction Scale (SAPS).

At the conclusion of the telephone call, site staff should:

- Remind subjects not utilizing the IWRS to return paper-based assessments to the site as soon as possible, but no later than 5 days, after completion of the assessment.
- If less than 112 days (16 weeks) have elapsed since the last dose of subcutaneous study medication in Study A4091061, remind female subjects of child-bearing potential of contraceptive requirements.
- Confirm the approximate timing of the next telephone call.

**106.4. Week 8 (Day 57 ± 5 days)**

Site staff should contact the subject via telephone to:

- Query for adverse events.
- Query for concomitant analgesic medication use (record dose, dosing regimen and reason for use).

At the conclusion of the telephone call, site staff should:

- If less than 112 days (16 weeks) have elapsed since the last dose of subcutaneous study medication in Study A4091061, remind female subjects of child-bearing potential of contraceptive requirements.
- Confirm the approximate timing of the next telephone call.

**106.5. Week 12 (Day 85 ± 5 days)**

Site staff should contact the subject via telephone to:

- Query for adverse events.

- Query for concomitant analgesic medication use (record dose, dosing regimen and reason for use).

- Query about physical rehabilitation activities subsequent to the total joint replacement surgery.

- Query for additional or corrective procedures related to the total joint replacement surgery.

During the telephone call, site staff should instruct the subject to complete the following assessments either via the IWRS or via paper, as established at the Baseline Visit:

- Pain in Replaced Joint (11-point NRS).

- Functional status (WOMAC for subjects with a total knee or hip replacement or SPADI for subjects with a total shoulder replacement); NOTE: the WOMAC and SPADI should be completed in their entirety.

- Overall satisfaction with joint replacement surgery measured by the SAPS.

At the conclusion of the telephone call, site staff should:

- Remind subjects not utilizing the IWRS to return paper-based assessments to the site as soon as possible, but no later than 5 days, after completion of the assessment.

- If less than 112 days (16 weeks) have elapsed since the last dose of subcutaneous study medication in Study A4091061, remind female subjects of child-bearing potential of contraceptive requirements.

- Confirm the approximate timing of the next telephone call.

### 106.6. Week 16 (Day 113 ± 5 days)

Site staff should contact the subject via telephone to:

- Query for adverse events.

- Query for concomitant analgesic medication use (record dose, dosing regimen and reason for use).

At the conclusion of the telephone call, site staff should:

- If less than 112 days (16 weeks) have elapsed since the last dose of subcutaneous study medication in Study A4091061, remind female subjects of child-bearing potential of contraceptive requirements.

- Confirm the approximate timing of the next telephone call.

### 106.7. Week 20 (Day 141 ± 5 days)

Site staff should contact the subject via telephone to:

- Query for adverse events.
- Query for concomitant analgesic medication use (record dose, dosing regimen and reason for use).

At the conclusion of the telephone call, site staff should:

- Confirm the approximate timing of the next telephone call.

### 106.8. Week 24 (Day 169 ± 5 days)

Site staff should contact the subject via telephone to:

- Query for adverse events.
- Query for concomitant analgesic medication use (record dose, dosing regimen and reason for use).
- Query about physical rehabilitation activities subsequent to the total joint replacement surgery.
- Query for additional or corrective procedures related to the total joint replacement surgery.

During the telephone call, site staff should instruct the subject to complete the following assessments either via the IWRS or via paper, as established at the Baseline Visit:

- Pain in Replaced Joint (11-point NRS).
- Functional status (WOMAC for subjects with a total knee or hip replacement or SPADI for subjects with a total shoulder replacement); NOTE: the WOMAC and SPADI should be completed in their entirety.
- Overall satisfaction with joint replacement surgery measured by the SAPS.

At the conclusion of the telephone call, site staff should remind subjects not utilizing the IWRS to return paper-based assessments to the site as soon as possible, but no later than 5 days, after completion of the assessment.

### 106.9. Subject Withdrawal/Early Termination

Subjects may withdraw from this substudy at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures at a given study site.

If a subject cannot be contacted within the window for a scheduled visit, every effort should be made to contact the subject outside of the visit window. If a subject is thought to be lost to follow-up, the site must attempt to contact the subject with a minimum of 3 documented phone call attempts and, if phone calls are unsuccessful, a certified letter sent to the subject. All attempts to contact the subject and information received during the contact attempts must be documented in the subject's medical records. In any circumstance, every effort should be made to document the subject's outcome, if possible. The investigator should inquire about the reason for withdrawal, follow-up with the subject regarding any unresolved adverse events, query for any new adverse events, query about concomitant analgesic medication use, physical rehabilitation activities or corrective procedures related to the joint replacement surgery and request that the subject complete the following assessments via the IWRS tool or via paper, as established at the Baseline Visit:

- Pain in Replaced Joint (11-point NRS).
- Functional status (WOMAC for subjects with a total knee or hip replacement or SPADI for subjects with a total shoulder replacement) (WOMAC or SPADI).
- Overall satisfaction with joint replacement surgery measured by the SAPS.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

## 107. SUBSTUDY ASSESSMENTS

Every effort should be made to ensure that the required procedures are completed as described. However it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform a procedure. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a required procedure cannot be performed the investigator will document the reason for this and any corrective and preventive actions which he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

### 107.1. Surgeon's Assessment of Procedural Difficulty

Following the total joint replacement surgery, the orthopedic surgeon performing the surgery will be asked to answer the following question:

"Taking into consideration the subject's medical history and physical condition prior to surgery would you classify the operative procedure as:

- Uneventful; or
- Minor complications; or
- Major complications.

If the category of minor or major complications is chosen, the surgeon will be requested to specify the complication(s).

### 107.2. Pathology Specimens

Surgeons will be requested to ship pathology specimens from the total joint replacement surgery to a Central Laboratory for analysis. Detailed instructions for the shipping of pathology specimens will be provided. Identification of specimens of adequate quality, preparation and histopathologic examination of the specimens will be performed in a standardized manner by the Central Laboratory under the direction of an expert orthopedic pathologist. Pathology reports will generally be returned to the referring site within 7-10 days following completion of the report by the Central Laboratory.

### 107.3. Telephone-based Assessments

Post-surgery, subjects will be contacted monthly via telephone by study site personnel.

#### 107.3.1. Adverse Events

At each post-surgery telephone contact, subjects will be queried for the occurrence of adverse events. All adverse events reported by the subject must be recorded on the appropriate case report form (CRF).


Subjects reporting adverse events (any seriousness or severity) with preferred terms of bradycardia, syncope, orthostatic hypotension, anhidrosis or hypohidrosis should be further evaluated for the presence of sympathetic autonomic neuropathy. Subjects will be referred

for neurologic or cardiologic evaluation depending on symptom presentation and the investigator's assessment as to the specialist best able to evaluate the subject.

### 107.3.2. Concomitant Analgesic Medication

At each post-surgery telephone contact, subjects will be queried about concomitant analgesic medication usage including dose, dosing regimen and reason for use. This information should be recorded on the appropriate case report form (CRF).

### 107.3.3. Physical Rehabilitation Activities

At the Week 4, 12 and 24 post-surgery telephone contacts, subjects will be queried for physical rehabilitation activities related to the replaced joint. Specifically, subjects will be asked to respond yes or no to the following question:

"Are you participating in physical rehabilitation activities related to your replaced joint?"

Subjects will be queried for details if the answer to the question is yes. This information should be recorded on the appropriate case report form (CRF).

### 107.3.4. Additional or Corrective Procedures

At the Week 12 and 24 post-surgery telephone contacts, subjects will be queried for additional or corrective procedures related to the total joint replacement surgery. Specifically, subjects will be asked to respond yes or no to the following question:

"Have you been told by your orthopedic surgeon that additional or corrective procedures (for example a revision or implant replacement) are necessary for your total joint replacement?"

Subjects will be queried for details if the answer to the question is yes. If necessary, the orthopedic surgeon may be contacted to confirm/expand upon the information regarding additional or corrective procedures.

## 107.4. Web-based Assessments

### 107.4.1. Overall Satisfaction with Joint Replacement Surgery

The Self-Administered Patient Satisfaction Scale (SAPS) evaluates subject satisfaction with the outcome of hip and knee arthroplasty and was designed to be used in conjunction with other clinical measures and functional health status instruments to evaluate the results of hip and knee arthroplasty.

The scale consists of four items focusing on satisfaction with the extent of pain relief, improvement in ability to perform home or yard work, ability to perform recreational activities and overall satisfaction with joint replacement.

Specifically, subjects will be asked to respond to the following questions:

- How satisfied are you with the results of your surgery?
- How satisfied are you with the results of your surgery for improving your pain?

- How satisfied are you with the results of surgery for improving your ability to do home or yard work?

- How satisfied are you with the results of surgery for improving your ability to do recreational activities?

Items are scored on a 4-point Likert scale with response categories consisting of 'very satisfied' (100 points), 'somewhat satisfied' (75 points), 'somewhat dissatisfied' (50 points), and 'very dissatisfied' (25 points). The scale score is the unweighted mean of the scores from the individual items, ranging from 25 to 100 per item with higher scores indicating greater satisfaction.

Subjects will be requested to complete the SAPS at Weeks 4, 12, and 24 either via the IWRS or by paper if the subject does not have access to the internet via a desktop, laptop or tablet computer. When completed on paper, the subject will be requested to return the assessment to the site as soon as possible, but no later than 5 days, after completion of the assessment.

### 107.4.2. Pain in Replaced Joint

Average pain in the joint to be replaced (pre-surgery) and the replaced joint (post-surgery) will be assessed with an 11-point Numeric Rating Scale (NRS) ranging from zero (no pain) to 10 (worst possible pain).

Question:

Select the number that best describes your average pain in your (joint to be replaced or your replaced joint) the past 24 hours.

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| No Pain | | | | | | | | | | Worst Possible Pain |

At Baseline and at Weeks 4, 12 and 24 following total joint replacement surgery, subjects will be asked to indicate their average pain in the joint to be replaced (pre-surgery) or the replaced joint (post-surgery) via the IWRS or by paper if the subject does not have access to the internet via a desktop, laptop or tablet computer. When completed on paper, the subject will be requested to return the assessment to the site but no later than 5 days, after completion of the assessment.

### 107.4.3. Assessment of Functional Activity

Subjects undergoing total knee or hip replacement will be asked to complete the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) with the knee or hip that was replaced serving as the "index joint". Subjects undergoing total shoulder replacement will be asked to complete the Shoulder Pain and Disability Index (SPADI). Descriptions of these assessments are provided below.

### 107.4.3.1. WOMAC

Subjects who will be proceeding to total knee or hip arthroplasty will be requested to complete all subscales of the WOMAC (ie, pain, physical function and stiffness) at Baseline and Weeks 4, 12, and 24 following total joint replacement surgery either via the IWRS or by paper if the subject does not have access to the internet via a desktop, laptop or tablet computer. When completed on paper, the subject will be requested to return the assessment to the site but no later than 5 days, after completion of the assessment.

A copy of the WOMAC can be found in Appendix 17.

#### WOMAC Pain Subscale

The WOMAC Pain subscale is comprised of 5 questions regarding the amount of pain experienced due to OA in the index joint (selected study knee or hip) in the past 48 hours. **For this study, the index joint (selected study knee or hip) is defined as the joint to be or that has been replaced.** The WOMAC Pain subscale is calculated as the mean of the scores from the five individual questions, which may not be a whole (integer) number. The WOMAC Pain subscale NRS scores for each question, and the WOMAC Pain subscale score, range from 0 to 10, with higher scores indicating higher pain.

#### WOMAC Physical Function Subscale

The WOMAC Physical Function subscale is comprised of 17 questions regarding the degree of difficulty experienced due to arthritis in the index joint (selected study knee or hip) in the past 48 hours. **For this study, the index joint (selected study knee or hip) is defined as the joint to be or that has been replaced.** The WOMAC Physical Function subscale is calculated as the mean of the scores from the seventeen individual questions, which may not be a whole (integer) number. The WOMAC Physical Function subscale NRS scores for each question, and the WOMAC Physical Function subscale score, range from 0 to 10 with higher scores indicating worse function. This refers to the subject's ability to move around and perform usual activities of daily living.

#### WOMAC Stiffness Subscale

The WOMAC Stiffness subscale is comprised of 2 questions regarding the amount of stiffness experienced in the index joint (selected study knee or hip) in the past 48 hours. **For this study, the index joint (selected study knee or hip) is defined as the joint to be or that has been replaced.** The WOMAC Stiffness subscale is calculated as the mean of the scores from the two individual questions, which may not be a whole (integer) number. The WOMAC Stiffness subscale NRS scores for each question, and the WOMAC Stiffness subscale score, range from 0 to 10 with higher scores indicating more stiffness. Stiffness is defined as a sensation of decreased ease with which the subject moves the index knee or hip.

### 107.4.3.2. The Shoulder Pain and Disability Index (SPADI)

Subjects who will be proceeding to shoulder arthroplasty will be requested to complete both dimensions of the SPADI (ie, pain and function) at Baseline and Weeks 4, 12, and 24 following total joint replacement surgery either via the IWRS or by paper if the subject does

not have access to the internet via a desktop, laptop or tablet computer. When completed on paper, the subject will be requested to return the assessment to the site but no later than 5 days, after completion of the assessment.

The SPADI consists of two dimensions (pain and function). The pain dimension consists of five questions regarding the severity of an individual's pain. Functional activities are assessed with eight questions designed to measure the degree of difficulty an individual has with various activities of daily living that require upper extremity use. The scores from both dimensions are averaged to derive a total score from 0 (best) to 100 (worst).

A copy of the SPADI can be found in Appendix 18.

## 108. SUBSTUDY ADVERSE EVENT REPORTING

Refer to Section 8 of the A4091061 protocol.

## 109. SUBSTUDY DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for the summary and descriptive analyses of the data collected in this substudy will be documented in a Statistical Analysis Plan, which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

### 109.1. Sample Size Determination

This substudy is designed to collect information sufficient to describe the post-operative outcome of subjects who underwent a total knee, hip, or shoulder replacement while participating in Study A4091061. The number of subjects who will enroll in this substudy is unknown but is estimated to be less than 25 subjects. Also unknown is the distribution of subjects across treatment groups (ie, the treatment given in Study A4091061). Therefore, it is predicted that there will be insufficient statistical power to perform statistical inferential analyses. All analyses will be descriptive in nature. The data collected in this substudy will be combined with similar data collected in other tanezumab studies for further analysis. These aggregate analyses will be reported separately.

### 109.2. Analysis of Endpoints

Data from the substudy of subjects with total joint replacement of the knee, hip or shoulder will be presented at substudy Baseline or Day 1 (day of surgery) and each post-surgery visit using observed data (no imputation for missing data), and at Week 24 using Last Observation Carried Forward (LOCF) for missing data. Data will be shown at the time points specified and also using change from (pre-surgery) Baseline where relevant. Data will be shown overall, and split by treatment group.

For the Surgeon's Assessment of Procedural Difficulty, the number and percentage of subjects in each category (Uneventful, Minor complications, Major complications) will be presented. Complications reported by the surgeon will be listed.

For the Subject's Overall Satisfaction with Surgery assessments (using the Self-Administered Patient Satisfaction scale, SAPS), the responses [score] for each category (Very Satisfied [100], Somewhat Satisfied [75], Somewhat Dissatisfied [50], Very Dissatisfied [25]) will be summarized for each of the four items. The scale score is the un-weighted mean of the scores from the individual items, ranging from 25 to 100 per item with higher scores indicating greater satisfaction. This total score will be summarized. Reponses to the question "How satisfied are you with the results of your surgery?" will also be summarized as satisfied (very satisfied and somewhat satisfied categories combined) and dissatisfied (somewhat dissatisfied and very dissatisfied categories combined).

Similarly, the number and percentage of subjects who have required (i) additional or corrective procedures related to their total joint replacement and (ii) participating in physical rehabilitation activities related to their replaced joint will be presented.

Average pain (NRS) in the replaced joint for all subjects, WOMAC Pain, Stiffness and Physical Function sub-scale scores for subjects who had total knee or hip replacement and SPADI Pain, function and total score for subjects who had total shoulder replacement will be summarized (including change from substudy Baseline summaries).

The number and percent of subjects with specified post-surgical complications will be presented. The list of post-surgical complications will be derived from reported adverse events and will consist of complications that are clinically significant and attributable to the total arthroplasty procedure eg, periprosthetic joint infection/wound infection, periprosthetic fracture, pulmonary embolism or sepsis/septicemia/shock. Literature reported analyses of post-surgical complications[9,10] will be used for guidance in developing the list of post-surgical complications. The list of post-surgical complications will be developed prior to database lock.

### 109.3. Data Monitoring Committee (DMC)

Refer to Section 9.7 of the A4091061 protocol.

### 109.4. External Adjudication Committee

External Adjudication Committee for the substudy will be as described for the main study. Refer to Section 9.5 of the A4091061 protocol.

## 110. SUBSTUDY QUALITY CONTROL AND QUALITY ASSURANCE

Refer to Section 10 of the A4091061 protocol.

## 111. SUBSTUDY DATA HANDLING AND RECORD KEEPING

Refer to Section 11 of the A4091061 protocol.

## 112. SUBSTUDY ETHICS

Refer to Section 12 of the A4091061 protocol.

## 113. SUBSTUDY DEFINITION OF END OF TRIAL

Refer to Section 13 of the A4091061 protocol.

## 114. SUBSTUDY SPONSOR DISCONTINUATION CRITERIA

Refer to Section 14 of the A4091061 protocol.

## 115. SUBSTUDY PUBLICATION OF STUDY RESULTS

Refer to Section 15 of the A4091061 protocol.

## 116. SUBSTUDY REFERENCES

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# WOMAC Osteoarthritis Index NRS3.1

## INSTRUCTIONS TO PATIENTS

In Sections A, B and C, questions will be asked in the following format and you should give your answers by putting an "✗ " in one of the boxes.

**EXAMPLES**:

1. If you put your "✗ "in the box on the far left as shown below, then you are indicating that you have **no** pain.

| No Pain | ✗ | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Pain |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

2. If you put your " ✗ "in the box on the far right as shown below, then you are indicating that you have **extreme** pain.

| No Pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | ✗ | Extreme Pain |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

3. Please note:
   a) that the further to the right you place your " ✗ " the **more** pain you feel.
   b) that the further to the left you place your " ✗ " the **less** pain you feel.
   c) **please do not** place your " ✗ "**outside any of the boxes.**

You will be asked to indicate on this type of scale the amount of pain, stiffness or disability you have felt during the last 48 hours.

Think about your _____ (study joint) when answering the questionnaire. Indicate the severity of your pain and stiffness and the difficulty you have in doing daily activities that you feel are caused by the arthritis in your _____ (study joint).

Your study joint has been identified for you by your health care professional.

If you are unsure which joint is your study joint, please ask before completing the questionnaire.

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**Section A**

**PAIN**

Think about the pain you felt in your _____ (study joint) caused by the arthritis during the last 48 hours.

*(Please mark your answers by putting an "X" in one of the boxes.)*

QUESTION: **How much pain have you had . . .**

1. when walking on a flat surface?

| No Pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Pain |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

2. when going up or down stairs?

| No Pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Pain |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

3. at night while in bed? (that is - pain that disturbs your sleep)

| No Pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Pain |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

4. while sitting or lying down?

| No Pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Pain |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

5. while standing?

| No Pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Pain |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

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***Section B***

**STIFFNESS** [redacted]

Think about the stiffness (not pain) you felt in your _____ (study joint) caused by the arthritis during the last 48 hours.

Stiffness is a sensation of **decreased** ease in moving your joint.

*(Please mark your answers by putting an "X" in one of the boxes.)*

6. How **severe** has your stiffness been **after you first woke up** in the morning?

| No Stiffness | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Stiffness |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

7. How **severe** has your stiffness been after sitting or lying down or while resting **later in the day**?

| No Stiffness | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Stiffness |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

[redacted]

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**Section C**

## DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities caused by the arthritis in your _____ (study joint) during the last 48 hours. By this we mean **your ability to move around and take care of yourself**.

*(Please mark your answers by putting an "✗" in one of the boxes.)*

QUESTION: **How much difficulty have you had . . .**

8. when going down the stairs?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

9. when going up the stairs?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

10. when getting up from a sitting position?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

11. while standing?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

12. when bending to the floor?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

13. when walking on a flat surface?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

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## DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities caused by the arthritis in your _____ (study joint) during the last 48 hours. By this we mean **your ability to move around and take care of yourself**.

*(Please mark your answers by putting an "✗" in one of the boxes.)*

QUESTION: **How much difficulty have you had . . .**

14. getting in or out of a car, or getting on or off a bus?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

15. while going shopping?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

16. when putting on your socks or panty hose or stockings?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

17. when getting out of bed?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

18. when taking off your socks or panty hose or stockings?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

19. while lying in bed?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

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## DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities caused by the arthritis in your _____ (study joint) during the last 48 hours. By this we mean **your ability to move around and take care of yourself**.

*(Please mark your answers by putting an "X" in one of the boxes.)*

QUESTION: **How much difficulty have you had . . .**

20. when getting in or out of the bathtub?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

21. while sitting?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

22. when getting on or off the toilet?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

23. while doing heavy household chores?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

24. while doing light household chores?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

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## Appendix 18. The Shoulder Pain and Disability Index (SPADI)

# Shoulder Pain and Disability Index (SPADI)

Please place a mark on the line that best represents your experience during the last week attributable to your shoulder problem.

### Pain scale

**How severe is your pain?**

Circle the number that best describes your pain where: 0 = no pain and 10 = the worst pain imaginable.

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| At its worst? | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| When lying on the involved side? | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Reaching for something on a high shelf? | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Touching the back of your neck? | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Pushing with the involved arm? | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

### Disability scale

**How much difficulty do you have?**

Circle the number that best describes your experience where: 0 = no difficulty and 10 = so difficult it requires help.

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Washing your hair? | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Washing your back? | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Putting on an undershirt or jumper? | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Putting on a shirt that buttons down the front? | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Putting on your pants? | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Placing an object on a high shelf? | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Carrying a heavy object of 10 pounds (4.5 kilograms) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Removing something from your back pocket? | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

## Appendix 19. France Appendix

This appendix applies to study sites located in France.

1. GCP Training

Prior to enrollment of any subjects, the investigator and any sub-investigators will complete the Pfizer-provided Good Clinical Practice training course ("Pfizer GCP Training") or training deemed equivalent by Pfizer. Any investigators who later join the Study will complete the Pfizer GCP Training or equivalent before performing Study-related duties. For studies of applicable duration, the investigator and sub-investigators will complete Pfizer GCP Training or equivalent every three years during the term of the Study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

2. Investigational Product

No subjects or third-party payers will be charged for investigational product.

3. Inspections

The investigator(s) will notify Pfizer or its service provider immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its service provider to prepare the study site for the inspection and will allow Pfizer or its service provider (if not prohibited by law) to be present during the inspection. The study site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its service provider. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its service provider with an opportunity to review and comment on responses to any such findings.