



## CLINICAL PROTOCOL

### **A PHASE 3 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY OF THE ANALGESIC EFFICACY AND SAFETY OF A DOSE TITRATION REGIMEN FOR THE SUBCUTANEOUS ADMINISTRATION OF TANEZUMAB IN SUBJECTS WITH OSTEOARTHRITIS OF THE HIP OR KNEE**

<b>Compound:</b>	PF-04383119
<b>Compound Name:</b>	Tanezumab
<b>US IND Number:</b>	BB-IND 11,680
<b>European Clinical Trial Database (EudraCT) Number:</b>	2013-002222-23
<b>Protocol Number:</b>	A4091056
<b>Phase:</b>	3

This document contains confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing this document, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.

0909077671e08f6a28c15516p1tdvradflA\aprisovered00n.124.Fath-2019 08:28 (GMT)

## Document History

## Document History

PFIZER CONFIDENTIAL  
Page 3

		<ul style="list-style-type: none"> <li>• Use of E-DMC instead of DMC throughout to reflect use of an “external” DMC.</li> <li>• Table of content moved to before Protocol Summary.</li> <li>• Template standard wording updates: Schedule of activities (list of abbreviations used in table added in table footnote), Section 4 Paragraph 1, inclusion criterion #9, exclusions #36-37; Section 4.4 (childbearing potential definition, post-menopausal status and requirements for contraceptives), Section 4.5 (new section “Sponsor Qualified Medical Personnel”), Section 5 (section restructured and language updated, definition of investigational product), Section 5.6 (new wording regarding storage conditions and reporting of protocol deviations), Section 5.7.1 (destruction of investigational product), Section 8 (updated language throughout), Medication Error section moved to Section 8.4, Section 10 (site to notify sponsor of regulatory inspections), Section 12.3 (subject privacy), Section 12.4 (sponsor review of recruitment materials), Section 15 (Publication of Study Results language updated).</li> <li>• Moved Patient-Level stopping rules from 3.1 to new Section: 7.4 “Triggered Events”.</li> <li>• Female of child-bearing potential wording updated.</li> <li>• Serum FSH testing Section 7.3.3.4 adjusted for consistency with template.</li> <li>• Word “rationale” added to column header in Summary of Changes “and Rationale”.</li> <li>• Added list of abbreviations (Appendix 13).</li> </ul> <p>Other administrative changes for clarification and consistency across protocols and the tanezumab program (eg, adjustment to wording and descriptions, removed redundancies, removed instructions for PK, NGF, biomarkers and ADA sample collection and processing, moved inclusion criteria assessed at baseline to 4.3 randomization criteria, deleted Appendix 4, spelling out of abbreviations, removed reference to worksheets, added EudraCT number and protocol summary.</p>
Final Protocol	27 July 2012	N/A

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



## TABLE OF CONTENTS

LIST OF TABLES .....	11
LIST OF FIGURES .....	11
APPENDICES .....	11
1. INTRODUCTION .....	23
1.1. Mechanism of Action/Indication.....	23
1.2. Background and Rationale .....	23
1.2.1. Role of Nerve Growth Factor in the Modulation of Pain .....	23
1.2.2. Description of Investigational Product .....	23
1.2.3. Overview of Clinical Studies .....	23
1.2.3.1. Overview of Efficacy in Osteoarthritis Clinical Studies .....	25
1.2.3.2. Overview of Safety in Clinical Studies .....	26
1.2.3.3. Subcutaneous Administration of Tanezumab in Clinical Studies .....	28
1.2.3.4. Joint Safety .....	30
1.2.4. Dose Selection Rationale .....	31
1.2.5. Rationale for Placebo Treatment .....	32
1.2.6. Rationale for Population .....	32
2. STUDY OBJECTIVES AND ENDPOINTS .....	32
2.1. Objectives .....	32
2.2. Endpoints.....	33
2.2.1. Primary Endpoints .....	33
2.2.2. Secondary Endpoints .....	33
2.2.3. Tertiary Endpoints .....	35
3. STUDY DESIGN.....	35
4. SUBJECT SELECTION .....	39
4.1. Inclusion Criteria.....	39
4.2. Exclusion Criteria.....	41
4.3. Randomization Criteria .....	45
4.4. Life Style Guidelines.....	45
4.5. Sponsor Qualified Medical Personnel.....	46
5. STUDY TREATMENTS.....	47

5.1. Allocation to Treatment .....	47
5.2. Breaking the Blind .....	47
5.3. Subject Compliance.....	48
5.4. Investigational Product Supplies .....	48
5.4.1. Dosage Form(s) and Packaging .....	48
5.4.1.1. Tanezumab .....	48
5.4.1.2. Placebo for Tanezumab .....	48
5.4.1.3. Acetaminophen (rescue medication) .....	48
5.4.2. Preparation and Dispensing .....	48
5.5. Administration.....	49
5.6. Investigational Product Storage .....	49
5.7. Investigational Product Accountability .....	50
5.7.1. Destruction of Investigational Product Supplies .....	50
5.8. Concomitant Medication(s).....	50
5.8.1. Prohibited Medications .....	50
5.8.2. Permitted Medications .....	51
5.9. Rescue Medication .....	52
6. STUDY PROCEDURES .....	53
6.1. Screening.....	54
6.2. Washout Period .....	56
6.3. Initial Pain Assessment Period (IPAP).....	57
6.4. Baseline Visit (Day 1).....	57
6.4.1. Pre-Randomization: Assessment of Randomization Criteria .....	57
6.4.2. Randomization .....	58
6.4.3. Pre-dosing (Day 1).....	58
6.4.4. Dosing (Day 1) .....	59
6.4.5. Post Dosing (Day 1).....	59
6.5. Week 2.....	59
6.6. Week 4.....	60
6.7. Week 8.....	61
6.7.1. Predosing (Week 8) .....	61
6.7.2. Dosing (Week 8).....	62

PFIZER CONFIDENTIAL  
Page 7

7.2.2. Patient’s Global Assessment of Osteoarthritis .....	75
7.2.3. Work Productivity and Activity Impairment Questionnaire - Osteoarthritis – Knee or Hip V2.0 (WPAI:OA).....	76
7.2.4. EuroQol 5 Dimension (EQ-5D-5L) .....	76
7.2.5. Assessment of Health Care Resource Utilization (HCRU) .....	76
7.3. Safety Assessments .....	77
7.3.1. Physical Examination .....	77
7.3.1.1. General Physical Examination .....	77
7.3.1.2. Musculoskeletal History and Physical Examination .....	77
7.3.2. Screening Numeric Pain Scale Rating (NRS) .....	77
7.3.3. Laboratory Safety Assessments .....	77
7.3.3.1. Blood Tests .....	78
7.3.3.2. Urinalysis and Urine Toxicology Screen .....	78
7.3.3.3. Pregnancy Testing .....	79
7.3.3.4. Serum FSH Testing .....	79
7.3.4. Vital Signs .....	80
7.3.4.1. Orthostatic Blood Pressure Measurement .....	80
7.3.5. 12-lead Electrocardiogram.....	81
7.3.6. Survey of Autonomic Symptoms.....	82
7.3.7. Radiographic Assessments .....	82
7.3.7.1. Radiation Exposure .....	83
7.3.8. Neurologic Examination.....	84
7.3.9. Anti-Drug Antibody Testing.....	84
7.4. Triggered Events and Subject-Level Stopping Rules .....	85
7.4.1. Dysesthesia/Allodynia .....	85
7.4.2. Hypersensitivity or Injection Site Reactions .....	85
7.4.3. Orthostatic Hypotension and Sympathetic Function Adverse Events .....	85
7.4.4. Evaluation and Follow-up for Increased, Severe Persistent Joint Pain .....	89
7.4.5. Central Reader and Subject-Level Stopping Criteria for Joint Safety Events.....	90
7.4.6. Procedures for Subjects Undergoing Joint Replacement.....	90
7.5. Pharmacokinetic (PK) and Pharmacodynamic (PD).....	90
7.5.1. Plasma for Analysis of Tanezumab .....	90

7.5.2. Nerve Growth Factor (NGF) for Pharmacodynamic Analyses .....	91
7.6. Biomarkers .....	91
7.6.1. Serum Biomarkers .....	91
7.6.2. Urine Biomarkers.....	92
7.7. Banked Biospecimens .....	93
7.7.1. Markers of Drug Response .....	93
7.7.2. Additional Research.....	94
8. ADVERSE EVENT REPORTING.....	94
8.1. Adverse Events.....	94
8.2. Reporting Period .....	95
8.3. Definition of an Adverse Event.....	95
8.4. Medication Errors.....	96
8.5. Abnormal Test Findings.....	96
8.6. Serious Adverse Events.....	97
8.6.1. Protocol-Specified Serious Adverse Events .....	98
8.6.2. Potential Cases of Drug-Induced Liver Injury.....	98
8.7. Hospitalization .....	99
8.8. Severity Assessment.....	100
8.9. Causality Assessment.....	101
8.10. Exposure During Pregnancy.....	101
8.10.1. Additional Postnatal Development Follow-Up .....	102
8.11. Occupational Exposure .....	102
8.12. Withdrawal Due to Adverse Events (See Also Section 6.16 Subject Withdrawal).....	103
8.13. Eliciting Adverse Event Information .....	103
8.14. Reporting Requirements.....	103
8.14.1. Serious Adverse Event Reporting Requirements .....	103
8.14.2. Non-Serious Adverse Event Reporting Requirements .....	104
8.14.3. Medical Device Complaint Reporting Requirements.....	104
8.14.4. Sponsor's Reporting Requirements to Regulatory Authorities .....	104
9. DATA ANALYSIS/STATISTICAL METHODS.....	104
9.1. Sample Size Determination.....	104

0909077671e08fa28-15510 pfdradfa\approved\00n.240.Fatt-2019 08:28 (GMT)

9.2. Efficacy Analysis .....	105
9.2.1. Analysis of Primary Endpoint .....	105
9.2.2. Analysis of Secondary Endpoints .....	106
9.3. Safety Analysis.....	108
9.3.1. Anti-Tanezumab Antibodies (ADA) .....	109
9.4. Analysis of Other Endpoints .....	110
9.4.1. Pharmacokinetic Data .....	110
9.4.2. Pharmacodynamic (NGF) Data .....	110
9.4.3. Biomarker Data.....	110
9.5. External Adjudication Committee.....	110
9.6. Data Monitoring Committee .....	111
9.6.1. Protocol-Level Rules for Dosing Suspension/Safety Assessment.....	112
9.6.1.1. Serious Adverse Events.....	112
9.6.1.2. Events Consistent with Hy’s Law .....	113
9.6.1.3. Joint Safety Events .....	113
10. QUALITY CONTROL AND QUALITY ASSURANCE.....	114
11. DATA HANDLING AND RECORD KEEPING .....	114
11.1. Case Report Forms/Electronic Data Record .....	114
11.2. Record Retention.....	115
12. ETHICS.....	115
12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) .....	115
12.2. Ethical Conduct of the Study .....	116
12.3. Subject Information and Consent.....	116
12.4. Subject Recruitment .....	117
12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP .....	117
13. DEFINITION OF END OF TRIAL.....	117
13.1. End of Trial in a Member State .....	117
13.2. End of Trial in all Other Participating Countries .....	117
14. SPONSOR DISCONTINUATION CRITERIA .....	117
15. PUBLICATION OF STUDY RESULTS .....	118
15.1. Communication of Results by Pfizer .....	118

15.2. Publications by Investigators .....	118
16. REFERENCES .....	120

## LIST OF TABLES

Table 1. SCHEDULE OF ACTIVITIES .....	18
Table 2. Adverse Drug Reactions in Subjects Receiving Tanezumab .....	27
Table 3. Blood and Urine tests.....	78
Table 4. Orthostatic Blood Pressure Changes and Subject Management.....	81

## LIST OF FIGURES

Figure 1. Follow-up Procedures for Confirmed Orthostatic Hypotension Events.....	88
--	----

## APPENDICES

Appendix 1. American College of Rheumatology (ACR) Classification Criteria for Osteoarthritis.....	124
Appendix 2. American Society of Anesthesiologists (ASA) Physical Status Classification .....	125
Appendix 3. Half-Lives of Prohibited Prior and Concomitant Medications .....	126
Appendix 4. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).....	130
Appendix 5. Patient's Global Assessment of Osteoarthritis.....	136
Appendix 6. Work Productivity and Activity Impairment Questionnaire: Osteoarthritis of the Knee or Hip V2.0 (WPAI:OA).....	137
Appendix 7. EuroQol 5 Dimension (EQ-5D-5L) .....	139
Appendix 8. Neuropathy Impairment Score (NIS) Sample .....	141
Appendix 9. Patient Health Questionnaire (PHQ-9).....	143
Appendix 10. Adjudication Categories.....	144
Appendix 11. Survey of Autonomic Symptoms (SAS) <sup>55</sup> .....	145
Appendix 12. Health Care Resource Utilization.....	146
Appendix 13. Abbreviations .....	148

0909077671e08fa28c15510p100MedVAApprovedOn: 24 Feb 2019 08:28 (GMT)

## Background

In 2010, the US Food and Drug Administration's (FDA) Division of Analgesia, Anesthetic, and Addiction Products (DAAAP) placed tanezumab (June/July 2010) and subsequently the entire NGFI class (December 2010) on partial clinical hold due to adverse events initially described by investigators as osteonecrosis that in some cases resulted in total joint replacement. Pfizer voluntarily imposed the partial clinical hold on study conduct in all countries.

Extensive analyses of the reports of osteonecrosis and other total joint replacements were conducted.<sup>1</sup> On March 12, 2012, the FDA Arthritis Advisory Committee reviewed these results as well as those prepared by the FDA.<sup>2,3</sup> The committee endorsed continued clinical development of the NGFI class of compounds with additional measures to minimize the risk and further protect subject safety. On August 28, 2012, the FDA lifted the partial clinical hold on tanezumab allowing the resumption of clinical studies for osteoarthritis and all other chronic pain conditions.

Risk mitigation measures were developed using recommendations from discussions with European agencies [United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA), Germany's Paul Ehrlich Institute (PEI) and Spain's Agency on Medicinal Products and Medical Devices (AEMPS)] as well as the FDA Arthritis Advisory Committee and interactions with FDA. They are incorporated in the design and objectives of the current study.

The FDA placed another partial clinical hold on the tanezumab clinical development program as well as all anti-NGF antibody studies in December 2012 due to concerns about adverse changes in the sympathetic nervous system of mature animals. Only studies in patients with cancer pain were allowed to continue.

In animal studies in rats and non-human primates, tanezumab treatment for up to 6 months, with doses producing greater systemic exposure than observed with clinical doses, was associated with lower sympathetic ganglion volume and lower average size of post-ganglionic sympathetic neurons when compared to control animals. All effects were completely reversible following a dosing-free recovery period. In a separate cardiovascular



Although evidence of clinically important effects on the sympathetic nervous system have not been identified in previously completed tanezumab studies, per agreement with the FDA, this and other clinical studies of tanezumab will incorporate additional safety measures to monitor for and manage subjects who may develop evidence of clinically important sympathetic nervous system dysfunction.

In order to optimize the potential benefit-risk relationship, the study will be conducted in subjects with moderate to severe osteoarthritis who have had inadequate pain relief with previous conventional pharmacological treatment options for osteoarthritis or are unable to take these pain medications due to contraindication or inability to tolerate them and are seeking effective treatment options other than/or prior to joint replacement surgery.

## Primary Objective

- ## Secondary Objectives

- ## Primary Endpoints

- Change from Baseline to Week 16 in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain subscale;
- Change from Baseline to Week 16 in the WOMAC Physical Function subscale;
- Change from Baseline to Week 16 in the Patient's Global Assessment of Osteoarthritis.

## Secondary Endpoints

### Efficacy:

- WOMAC Pain subscale change from Baseline to Weeks 2, 4, 8, 12 and 24;
- WOMAC Physical Function subscale change from Baseline to Weeks 2, 4, 8, 12 and 24;
- Patient's Global Assessment of Osteoarthritis (5-point Likert scale) change from Baseline to Weeks 2, 4, 8, 12 and 24;
- OMERACT-OARSI responder index at Weeks 2, 4, 8, 12, 16 and 24;
- Treatment Response: Reduction in the WOMAC Pain subscale of  $\geq 30\%$ ,  $\geq 50\%$ ,  $\geq 70\%$  and  $\geq 90\%$  at Weeks 2, 4, 8, 12, 16 and 24;
- Cumulative distribution of percent change from Baseline in the WOMAC Pain subscale score to Week 16 (endpoint for summary only);
- Treatment Response: Reduction in the WOMAC Physical Function subscale of  $\geq 30\%$ ,  $\geq 50\%$ ,  $\geq 70\%$  and  $\geq 90\%$  at Weeks 2, 4, 8, 12, 16 and 24;
- Cumulative distribution of percent change from Baseline in the WOMAC Physical Function subscale score to Week 16 (endpoint for summary only);
- Treatment Response: Improvement of  $\geq 2$  points in Patient's Global Assessment of Osteoarthritis at Weeks 2, 4, 8, 12, 16 and 24;
- Average pain score in the index joint change from Baseline to Weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24;
- WOMAC Stiffness subscale change from Baseline to Weeks 2, 4, 8, 12, 16 and 24;
- WOMAC Average change from Baseline to Weeks 2, 4, 8, 12, 16 and 24;
- WOMAC Pain Subscale Item: Pain When Walking on a Flat Surface, change from Baseline to Weeks 2, 4, 8, 12, 16 and 24;
- WOMAC Pain Subscale Item: Pain When Going Up or Down Stairs, change from Baseline to Weeks 2, 4, 8, 12, 16 and 24;
- Work Productivity and Activity Impairment Questionnaire for Osteoarthritis (WPAI:OA) impairment scores change from Baseline to Week 16;
- EuroQol 5 Dimension (EQ-5D-5L™) dimensions and overall health utility score at Baseline, Week 8 and Week 16;



- tanezumab 2.5 mg (Day 1) and tanezumab 2.5 mg (Week 8);
- tanezumab 2.5 mg (Day 1), and tanezumab 5 mg (Week 8);
- placebo to match tanezumab (Day 1) and placebo to match tanezumab (Week 8).

This study is designed with a total post-randomization duration of 40 weeks and will consist of three periods: Screening (up to a maximum of 37 days), Double-blind Treatment (16 weeks, 6 in-clinic visits), and Safety Follow-up (24 weeks).

The Screening Period (to begin up to 37 days prior to Randomization) includes a Washout Period (lasting a minimum of 2 days for all prohibited pain medications) if required, and an Initial Pain Assessment Period (IPAP, 7 days prior to Randomization/Baseline; minimum 3 days).

Rescue medication (acetaminophen) will be provided and may be taken if necessary, up to the maximum daily dose of 3000 mg per day but must be discontinued at least 24 hours prior to any in-clinic visit where efficacy assessments will be collected.

The Treatment Period ends and the Safety Follow-Up Period begins at the Week 16 visit. Subjects who are discontinued from treatment prior to Week 16, either at their request or at the decision of the investigator, will be required to undergo 24 weeks of follow-up (referred to as Early Termination Follow-Up). The 24 weeks of follow-up will be obtained through 3 clinic visits and monthly phone calls to yield 24-weeks of post-treatment follow-up.

Subjects who have undergone or plan to undergo total joint replacement or other arthroplasty procedure during the study will be discontinued from study treatment. Follow-up procedures for these subjects are described in [Section 6.16.2](#). In addition, subjects who undergo total knee, hip or shoulder joint replacement surgery during the study (Treatment Period or Follow-up Period) will be followed for 24 weeks after the procedure as part of a separate protocol, provided the subject consents (refer to [Section 6.17](#)).

## STATISTICAL METHOD

A sample size of approximately 230 subjects per treatment group is needed to provide approximately 90% power to achieve statistical significance (at the 5% two-sided level) for the two comparisons of tanezumab 2.5 and 2.5/5 mg SC versus placebo, over all three co-primary endpoints. The total sample size will be approximately 690 subjects.

The primary efficacy population will be the ITT (intent to treat) population, defined as all randomized subjects who received SC investigational product (either tanezumab or matching placebo). All treatment comparisons will use the two-sided 5% significance level.



**Table 1. SCHEDULE OF ACTIVITIES**[illegible]

09090757e02fa28d5a6phdVredVApersineedCdn.24-Oct-2019 08:28 (GMT)

PFIZER CONFIDENTIAL  
Page 20



[illegible]

Abbreviations: → or ---X--- = ongoing/continuous event, BMI = body mass index, BP = blood pressure, ECG = electrocardiogram, EQ-5D-5L = Euroqol – 5 dimensions – 5 levels, FSH = follicle stimulating hormone, HIV= human immunodeficiency virus, HR = heart rate, HCRU = healthcare resource utilization, IRT = interactive response technology, NRS = numerical rating scale, NSAID = non-steroidal anti-inflammatory agent, SAS = survey of autonomic symptoms, WPAI:OA = work productivity and activity index: osteoarthritis

- a. Day relative to start of study treatment (Day 1).
- b. The Screening Period begins up to 37 days prior to randomization and should allow for a minimum 2 day washout prior to entering the Initial Pain Assessment Period (IPAP) unless no washout is required. Screening x-rays should be obtained as early as possible in the Screening period to ensure that Central Reader confirmation of eligibility can be obtained within the 37-day Screening period (see [Section 7.3.7](#) for radiographic assessments). Subjects should preferably begin the IPAP once x-ray confirmation of radiographic eligibility has been obtained from the Central Reader. During the IPAP, diary entries (index joint pain and rescue medication use) must be provided for a minimum of 3 days. See [Section 6](#) for the order in which study procedures are to be conducted.
- c. All study activities at dosing visits (Baseline [Day 1] and Week 8), including sample collection, are performed prior to dosing, unless otherwise noted.
- d. At Screening, a comprehensive musculoskeletal medical history is obtained; see [Section 7.3.1.2](#) for details. History of insufficient pain relief from, inability to tolerate or contraindication to take acetaminophen, NSAIDs and tramadol or opioids should be collected. Any prior use of medications used to treat osteoarthritis and osteoarthritis pain and prior 30 day use for all other medications should also be collected.

- e. Only body weight is collected at Week 16 (End of Treatment).
- f. A musculoskeletal directed physical examination will be performed at each clinic visit; findings will be recorded on a case report form and findings considered clinically significant will be reported as adverse events. This physical examination is described in [Section 7.3.1.2](#)).
- g. Average pain in the shoulders, hips and knees or any other painful major joint with potential signs and symptoms of osteoarthritis that will be imaged at Screening.
- h. A neurological examination (NIS) will be performed by the Investigator (or designated physician) at each study visit and assessed for clinically significant changes from Baseline. Requirements for neurological consultation at which a full neurological examination is to be performed by a neurologist are detailed in [Section 7.3.8](#).
- i. FSH testing in female subjects as described in [Section 7.3.3.4](#). For female subjects of child-bearing potential, urine pregnancy tests are performed prior to dosing at dosing visits. Serum pregnancy tests are performed at Screening, Week 16 and Week 24 (or Early Termination, see [Section 6.16](#)).
- j. Blood samples for pharmacokinetics (PK) and pharmacodynamics (PD, NGF) at Weeks 2, 4 and 12 will only be collected in a subset of subjects.
- k. Biomarker samples in serum and urine should be collected CCI [REDACTED] at all scheduled time points, CCI [REDACTED] CCI [REDACTED]
- l. Pain in the index joint and rescue medication use are collected daily from the beginning of the IPAP to Week 16 (End of Treatment visit) though they may start as early as at the Screening visit, then are collected weekly until Week 40 (End of Study); see [Sections 7.1.1](#) and [7.1.2](#). Compliance with IRT assessments is to be reviewed at each study visit, including Phone visits.
- m. Assessment of pain in the non-index joints and NSAID use are collected weekly via IRT from the IPAP to the Week 40 visit ([Sections 7.1.1](#) and [7.1.3](#)). Post-baseline, subjects who indicate that they have experienced increased pain in a non-index major joint will rate the pain in that joint for the remainder of the study (see [Section 7.1.1](#)). The subject will also report any NSAID use weekly via IRT from the IPAP period to the Week 40 visit. NSAID, dosage and reason for use information will be obtained via phone calls or at clinic visits.
- n. The SAS questionnaire, WOMAC subscales, PGA of OA, WPAI:OA, HCRU and EQ-5D-5L will be administered using IRT at Study visits.
- o. Review of compliance and entries for joint pain scores, rescue medication and NSAID use entered by the subject via IRT. Rescue medication should be discontinued 24 hours prior to any clinic visit up to and including Week 24 (including during the Early Termination Follow-Up period, see [Section 6.16](#)). Subjects should return rescue medication bottles at each study visit for assessment of compliance.
- p. For female subjects of child-bearing potential; up to Week 24.
- q. If needed, following completion of the visit at which final efficacy assessments are collected (Week 24, 16 weeks after the last dose of investigational product administered), standard of care treatment (as described in [Section 5.8.2](#)) may be initiated, and usage recorded on the concomitant medication case report form (CRF). NSAID and acetaminophen use will still be recorded weekly via IRT during that period.
- r. The 24-week Safety Follow-Up period begins after completion of the End of Treatment visit. Subjects discontinuing the study at their request or at the decision of the Investigator prior to Week 16 should be withdrawn from treatment and begin the 24-week Early Termination Follow-Up period. As described in [Section 6.16](#) and [6.16.1](#), the follow-up period for subjects who terminate early includes 3 clinic visits and 2 telephone visits). Subjects who undergo total joint replacement will be followed for 24 weeks after the procedure as part of a separate protocol described briefly in [Section 6.17](#).

### 1.1. Mechanism of Action/Indication

## 1.2. Background and Rationale

Both interleukin (IL)-1 $\beta$  and tumor necrosis factor alpha (TNF- $\alpha$ ) have been shown to induce synthesis of NGF. Inhibition of NGF in turn blocks the hyperalgesia experienced after administration of these cytokines.<sup>7,8</sup> Together these observations suggest that NGF may play a role in pain secondary to inflammation or injury.

Tanezumab is highly potent in sequestering NGF and preventing interaction with the trkA or p75 receptors. Tanezumab and/or the murine precursor have been shown to be an effective analgesic in nonclinical animal models of pathological pain including arthritis, cancer pain, and post-surgical pain models.<sup>11</sup>

Over 11,000 subjects participated in the tanezumab clinical program comprising 32 studies conducted as of September 2014. Approximately 9810 healthy volunteers or patients have been treated with tanezumab in non-cancer pain clinical studies. In patients treated with tanezumab monotherapy or tanezumab + NSAID in completed non cancer pain studies, treatment experience with tanezumab approximates 5900 patient years of treatment exposure.

Most of these studies were conducted in patients with osteoarthritis of the knee or hip. A total of 17 clinical studies (4 Phase 2 studies and 13 Phase 3 studies), were initiated to provide evidence of efficacy and safety of tanezumab with intravenous (IV) or SC administration for the relief of the signs and symptoms of osteoarthritis alone or in combination with non-steroidal anti-inflammatory agents (NSAIDs). Both IV and SC routes of administration with tanezumab at fixed dose levels of 2.5 mg, 5 mg, and 10 mg every 8 weeks were evaluated in Phase 3 clinical studies of osteoarthritis subjects. In the 4 Phase 2 studies of tanezumab in patients with osteoarthritis, weight based doses of tanezumab ranging from 3 µg/kg to 1000 µg/kg approximating fixed doses of 0.3 mg to 100 mg were administered.

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 pain conditions, and 2 Phase 2 studies were conducted in 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 up to 100 mg.

In 2010, the US Food and Drug Administration's (FDA) Division of Analgesia, Anesthetic, and Addiction Products (DAAAP) placed tanezumab (June/July 2010) and subsequently the entire NGFI class (December 2010) on partial clinical hold due to adverse events initially described by investigators as osteonecrosis that in some cases resulted in total joint replacement. Pfizer voluntarily imposed the partial clinical hold on study conduct in all countries. The conduct of Phase 2/3 studies in osteoarthritis or other chronic pain conditions was impacted to varying extents by the partial clinical hold placed on the tanezumab clinical development program in June/July 2010.

Extensive analyses of the reports of osteonecrosis and other total joint replacements were conducted.<sup>1</sup> On March 12, 2012, the FDA Arthritis Advisory Committee reviewed these results as well as those prepared by the FDA.<sup>2,3</sup> The committee endorsed continued clinical development of the NGFI class of compounds with additional measures to minimize the risk and further protect subject safety. On August 28, 2012, the FDA lifted the partial clinical hold on tanezumab allowing the resumption of clinical studies for osteoarthritis and all other chronic pain conditions.

The FDA placed another partial clinical hold on the tanezumab clinical development program as well as all anti-NGF antibody studies in December 2012 due to concerns about adverse changes in the sympathetic nervous system of mature animals. Only studies in patients with cancer pain were allowed to continue. During 2013-2014, Pfizer conducted a comprehensive series of nonclinical studies to investigate the nonclinical effects on the sympathetic nervous system which led to the partial clinical hold (described in Section 5.3 of the tanezumab Investigators' Brochure).

0909077671e08f6a28c15516p10d7edf1A4091056Amendment 1, 23 September 2015 (GMT)

#### 1.2.3.1. Overview of Efficacy in Osteoarthritis Clinical Studies

The clinical significance of the reduction in pain with tanezumab treatment was assessed by the evaluation of subject responder rates using a categorical assessment of the WOMAC Pain subscale results, the OMERACT-OARSI<sup>17</sup> (Outcomes Measures in Arthritis Clinical Trials-Osteoarthritis Research Society International) Responder Index and a 2-grade or larger categorical improvement in the Patient's Global Assessment of Osteoarthritis. All responder analyses were determined with Baseline Observation Carried Forward (BOCF) imputation unless otherwise noted.



In studies A4091011 and A4091014, statistically significant response rates compared to placebo treatment were demonstrated at Week 16 with all tanezumab doses for the percentage of subjects with reductions in pain  $\geq 30\%$ ,  $\geq 50\%$ ,  $\geq 70\%$ , and  $\geq 90\%$  on the WOMAC Pain subscale in both studies with one exception (A4091011  $\geq 70\%$  reduction with tanezumab 2.5 mg vs placebo p-value was 0.053).

A prospectively defined analysis of subjects participating in Study A4091011, A4091014, A4091015, or A4091018 was performed to evaluate the efficacy of tanezumab with severe symptomatic osteoarthritis. Subjects defined with severe pain were those with a Baseline WOMAC Pain score  $\geq 7$  and a WOMAC Physical Function score of  $\geq 7$  and a score of “poor” or “very poor” in the Patient’s Global Assessment of Osteoarthritis. Of the 2979 subjects enrolled across the 4 studies, 742 (25.1%) met these criteria for severe disease. Tanezumab 5 mg and 10 mg provided significant and clinically meaningful benefit in this severe subject cohort when compared to placebo treatment.

A key objective of Study A4091015 and A4091018 was to compare the efficacy of tanezumab 5 mg and 10 mg versus naproxen 500 mg twice daily (BID) for the symptomatic treatment of osteoarthritis. To control the type 1 error rate for multiple comparisons, fixed sequence (step down) testing and the Hochberg procedure were predefined to begin with the highest dose (tanezumab 10 mg) followed by tanezumab 5 mg. As a result, despite replicate statistically significant differences with tanezumab 5 mg versus naproxen across 3 co-primary endpoints, a total of 6 comparisons, it is only possible to conclude statistically that tanezumab was superior to naproxen with respect to WOMAC Physical Function in both studies and the Patient’s Global Assessment of Osteoarthritis in one study.

In Study A4091030,<sup>18</sup> a key objective was to demonstrate that tanezumab 5 mg and tanezumab 10 mg were superior, or at a minimum non-inferior, to oxycodone controlled release (CR) 10-40 mg every 12 hours in the treatment of osteoarthritis. This objective was achieved. All four comparisons were statistically significant at Week 8; non-inferiority of tanezumab 10 mg versus oxycodone CR, superiority of tanezumab 10 mg versus oxycodone CR (p=0.018), non-inferiority of tanezumab 5 mg versus oxycodone CR, and superiority of tanezumab 5 mg versus oxycodone CR (p<0.001). In this study, oxycodone CR failed to separate from placebo treatment across all response measures at Week 8. Treatment with tanezumab 10 mg did not provide additional efficacy benefit above that observed with tanezumab 5 mg treatment.

In the largest safety and efficacy study, Study A4091025,<sup>19</sup> the addition of tanezumab 5 mg or 10 mg to NSAID treatment (ie, celecoxib 100 mg BID or naproxen 500 mg BID) did not provide substantial benefit over tanezumab 5 mg or 10 mg monotherapy, respectively. Only two statistically significant treatment differences were observed among the coprimary endpoint comparisons.

#### 1.2.3.2. Overview of Safety in Clinical Studies

Based on data from all subject populations who have received tanezumab in completed clinical studies to date, the adverse drug reactions listed in Table 2 are considered to be expected in subjects who are treated with tanezumab.

0909077671e08f6a28d45610p100Medf1A (approved) 001n. 24 Oct 2019 08:28 (GMT)

The majority of information regarding the safety profile of tanezumab comes from studies conducted in subjects with osteoarthritis. The safety profile observed in tanezumab to date in other chronic pain subject populations does not differ markedly from the results described below.

**Table 2. Adverse Drug Reactions in Subjects Receiving Tanezumab**

System Organ Class	Adverse Drug Reaction	Frequency <sup>2</sup>
Nervous system disorders	Burning sensation Carpal tunnel syndrome Hyperesthesia Hypoesthesia Paresthesia	Common
	Allodynia Peripheral neuropathy	Uncommon
Musculoskeletal and connective tissue disorders	Rapidly Progressive Osteoarthritis ( <i>in subjects with underlying osteoarthritis<sup>1</sup></i> )	Uncommon
	Arthralgia Joint swelling Myalgia Pain in extremity	Common
General disorders and administration site conditions	Peripheral edema	Common

<sup>1</sup> Rapidly Progressive Osteoarthritis may occur in subjects with underlying osteoarthritis. The frequency is estimated from adjudicated events of rapidly progressive osteoarthritis in historic clinical studies of tanezumab, which did not include specific risk minimization measures for this adverse reaction.

<sup>2</sup> Common ( $\geq 1\%$  and  $< 10\%$ ); Uncommon ( $\geq 0.1\%$  and  $< 1\%$ ).

A total of 7491 subjects were treated in 9 controlled Phase 3 osteoarthritis studies. The majority of these studies were conducted using IV administration of tanezumab; however, over 900 subjects were treated using SC administration in 2 studies. The adverse event profile of SC administration of tanezumab is comparable to that observed with the IV route based on the results of study A4091027<sup>20</sup> which compared SC versus IV administration in subjects with osteoarthritis. The incidence of adverse events, withdrawals due to adverse events, and serious adverse events in subjects treated with tanezumab monotherapy (5-10 mg) was similar to subjects receiving active comparator treatment and increased over placebo-treated subjects. In the tanezumab 2.5 mg monotherapy treatment group, the incidence of adverse events was similar to active comparator while the incidence of withdrawals due to adverse events and serious adverse events was similar to that of the placebo treatment group. Across the tanezumab monotherapy doses, the rates of adverse events, withdrawals due to adverse events, and serious adverse events were similar with tanezumab 5 mg and 10 mg, and elevated in comparison to tanezumab 2.5 mg. Tanezumab/NSAID combination therapy was associated with higher overall adverse event rates. The relationship of incidence to the dose of tanezumab administered was similar to that observed with tanezumab monotherapy.

Based on data from the Phase 3 osteoarthritis studies and results of an independent adjudication of investigator-reported adverse events of osteonecrosis and total joint

0909077671e08f6a28-11e5-8100-000119f89f3d Pfizer Inc. 29 Oct 2019 08:28 (GMT)

Among the most frequently reported adverse events in the controlled Phase 3 osteoarthritis studies, the incidence of peripheral edema, upper respiratory tract infection, fall, arthralgia, back pain, joint swelling, pain in extremity, hypoesthesia, and paresthesia tended to be higher in subjects receiving tanezumab monotherapy than subjects receiving either placebo or active comparator treatment. The incidence of peripheral edema, arthralgia, joint swelling, pain in extremity, and paresthesia increased with increasing doses of tanezumab monotherapy. The adverse events with increased incidence observed with active comparator over tanezumab monotherapy included the following: constipation, nausea, urinary tract infection, nasopharyngitis, osteoarthritis, and hypertension.

#### 1.2.3.2.1. Sympathetic Nervous System

Based on completed osteoarthritis studies where orthostatic blood pressure, heart rate deep breathing, or autonomic symptoms captured with the Neuropathy Symptom Change (NSC) questionnaire were specifically assessed, data are not suggestive of an adverse effect of tanezumab on autonomic function.

### 1.2.3.3. Subcutaneous Administration of Tanezumab in Clinical Studies

PFIZER CONFIDENTIAL  
Page 28



Study A4091027<sup>20</sup> was designed as a randomized, placebo-controlled study to demonstrate the efficacy and safety of tanezumab 2.5 mg, 5 mg, or 10 mg SC administered at 8-week intervals and the therapeutic equivalence of tanezumab 10 mg SC and tanezumab 10 mg IV administered at 8-week intervals in subjects with OA of the knee. Due to the clinical hold, enrollment was stopped prematurely and, therefore, was insufficient to yield adequate power to fulfill the primary objectives. The overall incidence of adverse events was comparable to that observed in previous tanezumab IV OA studies, and with the exception of injection-site reactions, the adverse event profile was comparable to that of previous tanezumab IV studies in subjects with OA. The higher incidence of injection-site reaction compared to other studies is likely due to the implementation of directed injection-site assessment – a procedure that was not a component of earlier tanezumab studies, which had included only IV administration of tanezumab. The majority of reported adverse events of injection-site reaction were mild, and none were severe. Across treatment groups, the incidence of serious adverse events and discontinuation due to adverse events was low.

PFIZER CONFIDENTIAL  
Page 29

#### 1.2.3.4. Joint Safety

Following the imposition of the clinical hold, a comprehensive investigation and analyses related to joint-safety were conducted, based on tanezumab monotherapy exposure in over 6400 subjects and tanezumab/NSAID combination therapy in 3400 subjects. There were over 5000 subjects who received tanezumab treatment alone or in combination with NSAIDs for 6 months or longer. The program was sufficient to define and characterize the adverse event of concern – rapidly progressive osteoarthritis – and evaluate the risk of rapidly progressive osteoarthritis in the context of the overall benefit-risk profile of tanezumab compared to standard of care. The results and conclusions regarding tanezumab and the other anti-NGF therapies are provided in detail elsewhere.<sup>1</sup>

After careful investigation, no evidence was found to substantiate that tanezumab is associated with an increased risk of osteonecrosis, a disease process quite distinct from osteoarthritis. A risk of rapidly progressive osteoarthritis was identified. The risk of rapidly progressive osteoarthritis with tanezumab monotherapy was well below that observed with tanezumab/NSAID combination therapy but greater than with placebo or active comparator treatment. A majority of subjects identified with rapidly progressive osteoarthritis had advanced osteoarthritis of the affected joint prior to treatment. The event rate of all-cause joint replacements in subjects with osteoarthritis was comparable among placebo, active comparator, and tanezumab monotherapy treatment groups.

On March 12, 2012 an FDA Arthritis Advisory Committee reviewed these results as well as those prepared by the FDA.<sup>2,3</sup> The Committee endorsed continued clinical development of the anti-nerve growth factor class of compounds with additional measures taken to minimize the risk and further protect subject safety. On August 28, 2012, the US FDA removed the partial clinical hold on tanezumab allowing the resumption of clinical studies for osteoarthritis and all other chronic pain conditions as related to joint safety.

Risk mitigation measures have been developed as an outgrowth of the joint-related safety analyses to reduce the risk of rapidly progressive osteoarthritis using recommendations from discussions with European agencies [United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA), Germany's Paul Ehrlich Institute (PEI) and Spain's Agency on Medicinal Products and Medical Devices (AEMPS)] as well as the FDA Arthritis Advisory Committee and interactions with FDA. These risk mitigation measures have been included in the tanezumab clinical program and those applicable to this study are outlined as follows:

**Risk Minimization:** (1) exclude chronic concomitant NSAID use, (2) exclude tanezumab doses that have been explored and do not demonstrate benefit over lower doses in the condition under study, (3) exclude subjects with evidence of rapidly progressive osteoarthritis or risk factors for such from participating in clinical studies, and (4) exclude subjects who are not suitable candidates for total joint replacement from study participation.

**Risk Identification and Management:** (1) evaluation and follow-up for severe persistent joint pain, (2) extended post-treatment follow-up, (3) a program-level Central Radiograph Reader and subject-level stopping criteria, (4) an Adjudication Committee, and (5) a Data Monitoring Committee (DMC) and protocol-level stopping rules.

#### 1.2.3.4.1. Rapidly Progressive Osteoarthritis

The pathophysiology of rapidly progressive osteoarthritis is not understood. Various mechanisms have been proposed including; ischemia, venous stasis, local nutritional deficiencies, synovitis, mechanical overloading, NSAID or corticosteroid use, intra articular deposition of hydroxyapatite or pyrophosphate crystals and subchondral insufficiency fractures.<sup>28,31,35,39,40.</sup>

#### 1.2.4. Dose Selection Rationale

PFIZER CONFIDENTIAL  
Page 31

### 1.2.5. Rationale for Placebo Treatment

### 1.2.6. Rationale for Population

Complete information for this compound may be found in the Single Reference Safety Document, which for this study is the Investigator's Brochure.

## 2. STUDY OBJECTIVES AND ENDPOINTS

## 2.1. Objectives

## Primary Objective

- Demonstrate superior efficacy of tanezumab 2.5 mg administered subcutaneously (SC) and tanezumab 2.5 mg SC titration to 5 mg SC versus placebo at Week 16.

## Secondary Objectives



- Average pain score in the index joint change from Baseline to Weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24;
- WOMAC Stiffness subscale change from Baseline to Weeks 2, 4, 8, 12, 16 and 24;
- WOMAC Average change from Baseline to Weeks 2, 4, 8, 12, 16 and 24;
- WOMAC Pain Subscale Item: Pain When Walking on a Flat Surface, change from Baseline to Weeks 2, 4, 8, 12, 16 and 24;
- WOMAC Pain Subscale Item: Pain When Going Up or Down Stairs, change from Baseline to Weeks 2, 4, 8, 12, 16 and 24;
- Work Productivity and Activity Impairment Questionnaire for Osteoarthritis (WPAI:OA) impairment scores change from Baseline to Week 16;
- EuroQol 5 Dimension (EQ-5D-5L™) dimensions and overall health utility score at Baseline, Week 8 and Week 16;
- Health Care Resource Utilization at Baseline, Week 24 and Week 40;
- Incidence and time to discontinuation due to Lack of Efficacy;
- Usage of rescue medication (incidence, number of days) during Weeks 2, 4, 8, 12, 16 and 24;
- Usage of rescue medication (amount taken) during Weeks 2, 4, 8, 12, and 16.

#### Safety Measures

- Adverse events;
- Standard safety assessments (safety laboratory testing [chemistry, hematology], sitting vital signs, ECG [12-lead]);
- Joint safety adjudication outcomes;
- Total joint replacements;
- Neurologic examination (Neuropathy Impairment Score [NIS]);
- Orthostatic (supine/standing) blood pressure assessments;
- Survey of Autonomic Symptom scores;
- Anti-drug antibody (ADA) assessments;

0909077671e08f6a28c4e5a0p0100redf1A (approved) On: 24 Feb 2019 08:28 (GMT)



- ### 2.2.3. Tertiary Endpoints

- Plasma tanezumab concentrations;
- Serum NGF assessments;
- Serum and urine osteoarthritis biomarker concentrations.

**Study Timeline**

**Study Groups:**

- Placebo (n = 230)
- tanezumab 2.5 mg (n = 230)
- tanezumab 2.5/ 5 mg (n = 230)

**Study Visits:**

Week	BL	2	4	8	12	16	24	40		
Day	-37	-7	1	15	29	57	85	113	169	281

**Key Events:**

- Initial Pain Assessment Period (IPAP):** Days -7 to -1 (diary)
- Randomization:** 1<sup>st</sup> dose study drug
- 2<sup>nd</sup> dose study drug:** titration time point for the 2.5/5mg arm
- End of Treatment; Primary Endpoint:** Week 16
- Safety Follow-Up:** Phone visit every 4 weeks; Week 24 efficacy visit
- End of Study; Final Visit:** Week 40

- tanezumab 2.5 mg (Day 1) and tanezumab 2.5 mg (Week 8);
- tanezumab 2.5 mg (Day 1), and tanezumab 5 mg (Week 8);
- placebo to match tanezumab (Day 1) and placebo to match tanezumab (Week 8).

1. Kellgren-Lawrence Grade 2 and Knee index joint;
2. Kellgren-Lawrence Grade 3 and Knee index joint;
3. Kellgren-Lawrence Grade 4 and Knee index joint;
4. Kellgren-Lawrence Grade 2 and Hip index joint;
5. Kellgren-Lawrence Grade 3 and Hip index joint;
6. Kellgren-Lawrence Grade 4 and Hip index joint.

This study is designed with a total (post-randomization) duration of 40 weeks and will consist of three periods: Screening (up to a maximum of 37 days), Double-blind Treatment (16 weeks, 6 in-clinic visits), and Safety Follow-up (24 weeks). The Screening Period (to begin up to 37 days prior to Randomization) includes a Washout Period (lasting a minimum of 2 days for all prohibited pain medications) if required, and an Initial Pain Assessment Period (IPAP; 7 days prior to Randomization/Baseline; minimum 3 days).

To be eligible for the study, subjects must have documented history indicating that previous treatment with acetaminophen, NSAIDs and either tramadol or opioids have not provided adequate pain relief, or that they could not be taken by the subject due to contraindication or inability to tolerate.

During the Screening Period all subjects will undergo knee, hip, and shoulder x-rays. Other major joints exhibiting signs or symptoms suggestive of osteoarthritis should also be imaged. A major joint is defined as a mobile synovial joint in the limbs such as the shoulders, elbows, wrists, hips, knees, ankle and excluding the joints of the toes and hands. All x-rays will be assessed by a Central Reader to determine subject radiographic eligibility for study participation. A pain score will be collected on an 11-point NRS via IRT for all joints for which a radiograph is obtained. Screening X-rays should be obtained as early as possible in the Screening period to facilitate completion of all required screening procedures within the 37-day Screening period.

In addition, the Screening Period will include the discontinuation and washout of all prohibited pain medications for at least 5 times the elimination half-life. The minimum washout period is 2 days for all prohibited medications that have an elimination half-life of less than 10 hours. Subjects who do not require a washout of prohibited pain medications may begin the IPAP preferably after x-ray confirmation of radiographic eligibility of the subject has been received from the Central Reader.

The Initial Pain Assessment Period, during which the daily average pain score in the index joint (scored with an 11-point numerical rating scale [NRS]) will be collected via Interactive



Response Technology (IRT), will begin up to 7 days prior to the Baseline (Day 1) randomization visit, and subjects must complete at least 3 diary entries during the IPAP period. Collection of other daily and weekly assessments via IRT is also performed during the IPAP.

During the Washout Period and the Initial Pain Assessment Period, subjects will be provided with rescue medication (acetaminophen) that may be taken if necessary, up to a maximum daily dose of 3000 mg per day, but must be discontinued at least 24 hours prior to the Baseline (Randomization) Visit.

Those subjects who qualify at the Baseline Visit (Day 1) will be randomized to 1 of 3 treatment groups.

Tanezumab 2.5 mg or placebo will be administered as a SC injection and the subject will be observed for adverse events including signs and symptoms of hypersensitivity in the clinic for a minimum of 1 hour after administration of investigational product. Subjects will return at Weeks 2 and 4 for interim visits and at Week 8 for the second administration of investigational product (placebo SC, tanezumab 2.5 mg SC or tanezumab 5 mg SC). The subjects will then return for clinic visits at Weeks 12 and 16.

The Week 16 visit marks both the end of the treatment period and the beginning of the 24-week Follow-up period. After completion of the Week 16 visit, subjects will be asked to return to the clinic for 2 additional study visits at Study Weeks 24 and 40. Between the clinic visits in the Follow-up period, subjects will be contacted by clinical research site staff at approximately monthly intervals to collect adverse event, concomitant drug and concomitant non-drug information.

At the Week 24 visit, (16 weeks after the last dose of investigational product which corresponds to more than 5 times the elimination half-life of tanezumab) general safety assessments and the last study efficacy assessments will be collected. Following this visit, standard of care treatment may be initiated. Standard of care treatment refers to approved analgesics used to relieve the pain of OA; these include opioids, topical analgesics, NSAIDs, capsaicin products, injectable corticosteroids and viscosupplementation (eg, hyaluronan) and are prescribed at the discretion of the investigator. Pre-specified analgesics will be reimbursed by Pfizer.

Subjects will then return for the Week 40 End of Study visit which marks completion of the Follow-Up period. At this visit, all End of Study procedures are to be completed, including repeat knee, hip, and shoulder x-rays as well as any additional major joint that was imaged at Screening or any at risk major joint (See [Section 7.4.4](#)) identified during the study period. The window for obtaining end of study x-rays is 30 days from the nominal time point of the visit. The Week 40 (End of Study) X-rays should be obtained as close as possible to the Week 40 visit, preferably before the visit and not more than 14 days after the Week 40 visit.

Continuing on from the Initial Pain Assessment Period, subjects will provide a daily assessment of their index joint pain and rescue medication use through Week 16 (End of Treatment) then weekly between Weeks 16 and 40 (End of Study) via IRT, using a 24-hour

The treatment period ends and the 24 week Safety Follow-up period begins at the Week 16 visit. Subjects who complete the Week 16 visit will be considered to have completed the Double-blind Treatment Period and will enter the 24-week Safety Follow-up period. Subjects who leave the study prior to completing the Week 16 visit will not be considered to have completed the Double-blind Treatment Period.

Subjects who complete the 24-week post treatment follow-up period (safety follow-up or Early Termination Follow-up) will be considered to have completed the study, whether the subject completed the treatment period or discontinued prior to completing the treatment period. Subjects who do not complete the 24 week post-treatment follow-up period will not be considered to have completed the study.

X-rays of the shoulders, knees and hips (both shoulders, both knees and both hips) 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. The remainder of efficacy and safety assessments should be done at the scheduled first visit which is to occur 8 weeks after the last dose of investigational product (as described in 6.16.1.1). 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 investigational product (which corresponds to more than 5 times the elimination half-life of tanezumab) to collect safety and efficacy data (as described in 6.16.1.3). Once the clinic visit 16-weeks after the last administration of investigational product has been completed and final efficacy assessments have been collected, standard of care treatment will be offered to subjects for the remaining 8 weeks of the required Follow-Up period. Standard of care treatment may be initiated as needed and should be recorded on the concomitant medication CRF. The third and final clinic visit should be scheduled to take place approximately 24-weeks after the subject received the last dose of investigational product. That visit (described in 6.16.1.5), will include repeat shoulder, knee and hip radiographs (and any other joint imaged at

In the event a subject refuses the Early Termination Safety Follow-up, or chooses to discontinue during the regularly planned Safety Follow-up period (after Week 16 and through Week 40), a complete early termination visit should be performed. This early termination visit should include all procedures scheduled for the Week 24 and Week 40 visits, unless the Week 24 visit has already been completed; in that case, only Week 40 procedures will be required. In addition, if the Week 16 visit was not completed prior to termination, a general physical examination, body weight, WPAI:OA and EQ-5D-5L will also be obtained. Female subjects of child-bearing potential will be advised to continue their contraception regimen during a period of 112 days (16 weeks) after the last dose of investigational product.

## 4. SUBJECT SELECTION

### 4.1. Inclusion Criteria

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

- PFIZER CONFIDENTIAL  
Page 39

- PFIZER CONFIDENTIAL  
Page 40

1. Subjects who are investigational site staff members directly involved in the conduct of the study 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 study.
2. Body Mass Index (BMI) of  $>39 \text{ kg/m}^2$ .
3. History of other disease that may involve the index joint including inflammatory joint disease such as rheumatoid arthritis, seronegative spondyloarthropathy (eg, ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease related arthropathy), crystalline disease (eg, gout or pseudogout), endocrinopathies, metabolic joint diseases, lupus erythematosus, joint infections, Paget's disease, or tumors.
4. Radiographic evidence of any of the following conditions in any screening radiograph as determined by the central radiology reviewer and as defined in the tanezumab program imaging atlas: excessive malalignment of the knee, severe chondrocalcinosis; other arthropathies (eg, rheumatoid arthritis), systemic metabolic bone disease (eg, pseudogout, Paget's disease; metastatic calcifications), large cystic lesions, primary or metastatic tumor lesions, stress or traumatic fracture.
5. Radiographic 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 fractures, 4) spontaneous osteonecrosis of the knee (SPONK), 5) osteonecrosis, or 6) pathologic fracture.
6. A history of osteonecrosis or osteoporotic fracture (ie, a subject with a history of osteoporosis and a minimally traumatic or atraumatic fracture).
7. History of significant trauma or surgery to a knee, hip, or shoulder within the previous year.
8. Planned surgical procedure during the duration of the study.
9. Largely or wholly incapacitated, (eg, subject bedridden or confined to a wheelchair, permitting little or no self-care).

10. Fibromyalgia, regional pain caused by lumbar or cervical compression with radiculopathy or other moderate to severe pain that may confound assessments or self-evaluation of the pain associated with osteoarthritis. Subjects with a present (current) history of sciatica are not eligible for participation. Subjects with a past history of sciatica who have been asymptomatic for at least one year and who have no evidence of radiculopathy or sciatic neuropathy on thorough neurologic examination are eligible participation.
11. Past history of carpal tunnel syndrome (CTS) with signs or symptoms of CTS in the one year prior to Screening.
12. Subjects considered unfit for surgery, defined as Grade >3 on the American Society of Anesthesiologists (ASA) physical classification system for surgery (see Appendix 2), or subjects who would not be willing to undergo joint replacement surgery if required.
13. History of intolerance or hypersensitivity to acetaminophen (paracetamol) or any of its excipients or existence of a medical condition or use of concomitant medication for which the use of acetaminophen is contraindicated (refer to product labeling).
14. Use of prohibited medications without the appropriate washout period (if applicable) prior to Screening or Initial Pain Assessment Period (refer to [Section 5.8.1](#)).
15. Oral or intramuscular corticosteroids within 30 days prior to the Initial Pain Assessment Period.
16. Intra-articular corticosteroid injection in the index joint within 12 weeks, or to any other joint within 30 days prior to the Initial Pain Assessment Period.
17. Intra-articular hyaluronic acid injection in the index joint within 30 days (or within 18 weeks for long-acting formulations such as Synvisc) prior to the Initial Pain Assessment Period.
18. History of cancer within 5 years prior to Screening, except for cutaneous basal cell or squamous cell cancer resolved by excision.
19. Signs and symptoms of clinically significant cardiac disease including but not limited to:
  - Ischemic cardiac disease (eg, unstable angina, myocardial infarction) in the 6 months prior to Screening;
  - Surgery or stent placement for coronary artery disease in the 6 months prior to Screening;



- Subjects with a history of heart block now controlled by a functioning cardiac pacemaker are eligible.

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

22. History, diagnosis, signs or symptoms of any clinically significant psychiatric disorder, including but not limited to:

- PFIZER CONFIDENTIAL  
Page 43



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

- PFIZER CONFIDENTIAL  
Page 44

- ### 4.3. Randomization Criteria

1. Subject must have completed appropriate washout of analgesics.
2. Subject must have made at least 3 pain diary entries in the 7 days prior to the Baseline (Day 1) visit.
3. Subject must have abstained from taking rescue medication (acetaminophen) within the 24 hours that precede dosing.
4. WOMAC Pain subscale NRS  $\geq 5$  in the index joint at Baseline.
5. WOMAC Physical Function subscale NRS  $\geq 5$  in the index joint at Baseline.
6. Patient's Global Assessment of Osteoarthritis must be "fair", "poor" or "very poor" at Baseline.
7. Review of the ECG and laboratory results and confirmation that there are no clinically significant or exclusionary findings.
8. Radiographic eligibility must have been confirmed by the Central Reader, including KL grade  $\geq 2$  in the index joint.

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.

Refer to [Section 5.8](#) and Appendix 3 for guidance on permitted and prohibited medications.

All female subjects who are of childbearing potential and are sexually active and at risk of pregnancy must agree to use two (2) methods of highly effective contraception consistently and correctly throughout 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 2 appropriate forms of contraception for the individual subject from the permitted list of contraception methods (see below), and instruct the subject in their consistent and correct use. Subjects need to affirm that they meet the criteria for correct use of at least two of 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 a selected contraceptive method is 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:

1. Established use of oral, inserted, injected, implanted or transdermal 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.
2. Correctly placed copper-containing intrauterine device (IUD).
3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.
4. Male sterilization with absence of sperm in the post-vasectomy ejaculate.
5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

#### **4.5. Sponsor 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 numbers, 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

0909077671@08Feb2019 15:53:00 (GMT) 0909077671@08Feb2019 08:28 (GMT)

subjects participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems, however it should be used only 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 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

Subjects will be randomized at Baseline to one of the following treatments:

Treatment Group
1. Placebo SC at Baseline and Week 8
2. Tanezumab SC 2.5 mg at Baseline and Week 8
3. Tanezumab SC 2.5 mg at Baseline and tanezumab SC 5 mg at Week 8

Subjects will be randomly assigned in a 1:1:1 ratio to the above treatment regimens according to a computer generated randomization code. As detailed in [Section 3](#), randomization will be stratified by index joint and most severe Kellgren-Lawrence grade (of any knee or hip joint). 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. The randomization code will be maintained by a person(s) who is independent of the trial conduct and produces the randomization code. 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 dispensable unit identification numbers (ie, the drug supply to be administered) from the IRT. Further details are provided in the Pharmacy Manual.

### 5.2. Breaking the Blind

This is a randomized, double-blind, parallel group study. The subjects, investigators, Study Coordinators, 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.

Blinding 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

0909077671e08fa28-15510 pfdrf1A approved 001n. 24 Feb 2019 08:28 (GMT)

### 5.3. Subject Compliance

Compliance with the use of rescue medication will be reviewed and reconciled at each study visit. Refer to [Section 5.9](#) for rules governing rescue medication use.

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

#### 5.4.1.1. Tanezumab

Tanezumab 5 mg is presented as a sterile solution for subcutaneous administration, in a glass pre-filled syringe (PFS). Each PFS contains a sufficient amount of tanezumab to provide the intended dose of drug at a concentration of 5 mg/mL.

#### 5.4.1.2. Placebo for Tanezumab

#### 5.4.1.3. Acetaminophen (rescue medication)

#### 5.4.2. Preparation and Dispensing

PFIZER CONFIDENTIAL  
Page 48

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 where facilities to handle allergic reactions are available. All subjects will receive 1 mL of investigational product 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.

Tanezumab and placebo will be shipped and stored at a temperature between 2° and 8°C and protected from light.

The investigator or an approved representative (eg, Pharmacist) will ensure that all investigational product is stored in a secure 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 drug label. See the Pharmacy Manual for storage conditions of the product.

Storage conditions stated in the single reference safety document (SRSD) (ie, investigator's brochure [IB]), will 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 the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. 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 the storage conditions, described in the labeling, 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 documentation of 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. Specific details regarding information the site should report for each excursion will be provided to the site.

## **5.7. Investigational Product Accountability**

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product(s).

### **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 destruction is authorized to take place at the study 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, and all destruction must be adequately documented.

## **5.8. Concomitant Medication(s)**

### **5.8.1. Prohibited Medications**

Use of analgesics (including marijuana) other than acetaminophen is prohibited throughout Week 24 of the study beginning 48 hours prior to the start of the Initial Pain Assessment Period or at the period of time prior to the start of the Initial Pain Assessment Period that is  $\leq 5$  times the half-life of the particular analgesic used, whichever is greater. Refer to Appendix 3: Half-Lives of Prohibited Prior and Concomitant Medications, for a detailed washout schedule for prohibited medications. This is not an exhaustive list and Pfizer study management should be consulted for assistance if needed, in determining whether or not specific medications are permitted. Sites must consult product labeling and conduct a taper according to the product instructions if a taper is required.

Use of prescription or over-the-counter (OTC) NSAIDs (including COX-2 selective inhibitors) is also prohibited except in the following circumstances. Limited concomitant use of prescription or OTC NSAID may be allowed on an occasional basis for self-limiting conditions not related to osteoarthritis however, they may not be taken within 48 hours (or 5 half-lives, whichever is greater) of a study visit where efficacy assessments are being collected. The study monitor or Pfizer clinician should be contacted for approval prior to use whenever possible, and all doses and days of use will be recorded on the concomitant analgesic CRF. NSAID use should not exceed a total of 30 days between Day 1 (Baseline) and Week 24. Beginning at Week 24 (16-weeks after the last dose of investigational product), subjects may use NSAIDs at their discretion.

Subjects will be instructed that many over-the-counter medications contain NSAIDs and to guard against overuse. Subjects will be instructed to keep a recording of NSAID usage and amount. The number of days of NSAID use will be collected weekly via IRT from Baseline (Day 1) through the Week 40 visit. Additional information regarding NSAID use such as medication names, dosage and reason for use will be collected by the site on a CRF.

0909077671e08fa28-15510 pfdrfdrfa4091056v000n.240-Conf-2019 08:28 (GMT)





to avoid scheduling prospective procedures such that pain medications would be needed within 48 hours of a study visit (24 hours for acetaminophen). Contact study management 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. Any use of NSAID must be consistent with the allowed limit described in the Prohibited Medications [Section 5.8.1](#) above.

For subjects who have discontinued investigational product, the investigator may prescribe standard of care treatment for subjects once the last efficacy assessments have been obtained at the visit occurring 16 weeks after the last dose of investigational product. In this study, standard of care treatment refers to analgesics approved by FDA (for US subjects) or another applicable Health Authority (for non-US subjects) and used to relieve the pain of OA. These medications include opioids, topical analgesics, NSAIDs, capsaicin products, injectable corticosteroids and viscosupplementation (eg, hyaluronan) and are prescribed at the discretion of the investigator. Pre-specified analgesics are not considered investigational product but will be reimbursed by Pfizer while the subject is participating in the Safety Follow-Up Period, beginning at Week 24. Their use will be recorded on the concomitant medication CRF.

### **5.9. Rescue Medication**

Acetaminophen will be issued to the subject by the study sites in its approved marketed product dress, (carton, bottle, documents) for use as rescue medication.

During the Washout Period and the Initial Pain Assessment Period, subjects may take rescue medication as needed for osteoarthritis or other types of pain or illness up to a maximum daily dose of 3000 mg per day. Rescue medication must be discontinued at least 24 hours prior to the Baseline (Randomization) visit.

In the event of inadequate pain relief for osteoarthritis during the treatment period (ie, after the Baseline [Randomization] visit through Week 16), subjects may take up to 3000 mg of acetaminophen per day but only up to 3 days per week. Subjects must discontinue rescue medication within 24 hours of any scheduled site visit at which efficacy assessments are collected.

From the Baseline (Randomization) visit through Week 16, subjects taking greater than 3 days per week of rescue medication (any level of acetaminophen used specifically for osteoarthritis pain) must be interviewed by study site personnel to determine if this is due to lack of efficacy or other reasons, and the discussion should be noted in the subject's source documents. Up to Week 16, subjects who have taken rescue medication more frequently than specified in the protocol and indicate that they cannot or will not follow the rescue medication protocol requirements because of insufficient osteoarthritis pain relief should be withdrawn from study treatment due to lack of efficacy and entered in the Early Termination Follow-Up period (See [Section 6.16](#)). Subjects who indicate that they anticipate being able to take rescue medication no more than 3 days per week going forward will be allowed to continue in the treatment period. However, if these subjects continue to take rescue

After the Week 16 visit subjects may take acetaminophen rescue medication daily, up to the maximum permitted dose of 3000 mg per day. After Week 24, subjects may be started on standard of care. After Week 24, subjects may continue to use acetaminophen as needed up to the maximum dose per day as permitted by local or national labeling.

All rescue medication must be discontinued at least 24 hours prior to any scheduled study visit at which efficacy data is collected (ie, up to the Week 24 visit or the Early Termination visit that occurs 16 weeks after the last dose of investigational product).

Subjects will be instructed that many over-the-counter medications contain acetaminophen, and to guard against overuse. Subjects will be instructed to keep a record of their acetaminophen rescue medication daily usage via the IRT through Week 16. After Week 16 and up to the Week 40 visit, usage of acetaminophen rescue medication will be recorded once weekly via the IRT. The dose and reason for acetaminophen use in instances other than as rescue medication must be recorded on the appropriate concomitant medication case report form (CRF).

The site monitor should be consulted in the event that site layout, logistics, or equipment require adjustment to the ordering of study procedures or resolution of technical difficulties to enable performance of the Protocol. Such changes will be implemented administratively and documented in the appropriate venue (eg, site trial documentation and/or clinical study report). As much as possible, each subject's clinic visit should be conducted at approximately the same time of day throughout their participation in the study.

Study visit windows are  $\pm 3$  days for Weeks 2 and 4, and  $\pm 7$  days for Weeks 8, 12, 16, 24 and 40 as well as for telephone visits at Weeks 20, 28, 32 and 36. In the event the subject

requires a visit within the extremes of the visit windows, following study visits should be scheduled with reference to the original baseline visit date. Subject scheduling issues should be brought to the attention of study management for resolution. Dosing visits should be targeted to occur no earlier than 8 weeks  $\pm$  7 days from the previous injection. Visit window for the Week 40 (End of study) x-rays is  $\pm$ 30 days from the nominal time point of the visit however they should preferably be obtained prior to the Week 40 visit and if possible, less than 14 days after the visit.

Subjects will be reminded to abstain from taking rescue medication 24 hours prior any study visit at which efficacy data is collected.

### 6.1. Screening

The Screening Period allows for completion of Screening procedures, including washout of prohibited medications, and completion of the Initial Pain Assessment Period (IPAP). The IPAP may begin once washout has been completed (if needed) and once x-ray confirmation that the selected index joint meets the KL grade criteria, and that no exclusionary conditions are present on X-ray has been obtained from the Central Reader. The total duration of the Screening period should not exceed 37 days.

Written informed consent will be obtained from each subject prior to any trial assessments. Each subject will be assessed as to his/her suitability per inclusion/exclusion criteria review.

Subject demographics and the date of OA diagnosis for every affected joint will be obtained. A comprehensive medical history and concomitant medication review will be performed for each subject; in addition, a comprehensive evaluation of musculoskeletal history and musculoskeletal physical exam will be performed (see 7.3.1.2). The index joint will be selected at the Screening visit based on pain scores. If bilateral knee and/or hip pain is present, the investigator will select the more painful joint as the study (index) joint. X-ray confirmation of eligibility (Kellgren-Lawrence Grade  $\geq$ 2 for selected index joint and absence of exclusionary conditions) will be obtained prior to the Baseline visit from the imaging Central Reader based on x-rays of each knee, hip and shoulder (and other major joint x-ray, if relevant) obtained at Screening. Anticipate that it may take up to two weeks to obtain X-ray confirmation from the central reader prior to the Baseline visit.

History of insufficient pain relief from, inability to tolerate or contraindication to take, acetaminophen, NSAID, and tramadol or opioid treatments will be clearly documented on the appropriate CRF page. The required level of evidence to establish that subjects meet this inclusion criterion will be based upon the investigator's judgment. Investigators should rely upon available medical records that he or she may already have access to, prescription medication records (eg, retail pharmacy records), records or information provided by referring physicians and/or subject historical recall if the investigator is satisfied with the level of detail subjects are able to provide on past medication use. Investigators should clearly document in source records the information used to establish whether a subject does or does not meet this inclusion criterion. As a guide, investigators should document medication names, medication doses, reasons for use, dates of use and reason for discontinuation. If one or more of the above medications could not be used due to

### Activities at Screening (Initial Screening Visit):

- NOTE:** Based on pain scores. If the subject experiences pain in more than one joint, then the most painful joint should be selected as the index joint. Radiographic eligibility of the selected index joint will need to be confirmed by the Central Reader;

- NOTE:** Subjects should be thoroughly instructed on completion of WOMAC scales, no coaching or other interpretative assistance should be given to subjects during completion of these questionnaires;

- PFIZER CONFIDENTIAL  
Page 55



- ## 6.2. Washout Period

PFIZER CONFIDENTIAL  
Page 56

If necessary, the Screening/Washout Period may be adjusted due to individual subject circumstances (eg, stabilization of a concomitant medication), contact study management for guidance. However, the total duration of the Screening period is not to exceed 37 days.

The Initial Pain Assessment Period will begin up to 7 days prior to the Randomization/Baseline Visit (Day 1) to allow subjects to complete at least 3 diary entries during the IPAP period.

Study sites will monitor the IRT reports for compliance with diary recordings and rescue medication use and reschedule those subjects who fail to provide 3 diary days or fail to refrain from rescue medication use 24 hours prior to baseline.

Assessment of pain in the major, non-index joints will be performed once during the IPAP. Subject will also be reminded of contraception requirements.

#### 6.4.1. Pre-Randomization: Assessment of Randomization Criteria

Subjects must continue to satisfy Inclusion/Exclusion Criteria (general criteria and those specific to the Baseline visit - See [Section 4.3](#)) to be eligible for Randomization. Full eligibility, including (but not limited to) confirmation of appropriate washout of concomitant medication, abstinence from acetaminophen in the previous 24 hours, completion of at least 3 diary entries in the past 7 days, subject meets required WOMAC Pain subscale Baseline score, subject meets required Baseline WOMAC Physical Function subscale and Patient's Global Assessment of Osteoarthritis scores, and that no adverse events occurred since the Screening visit that would render the subject ineligible for randomization, should be assessed before carrying out Randomization in the IRT system.

Subjects will undergo the following assessments prior to randomization:

- Inclusion/exclusion review (including results of ECG, laboratory and x-ray obtained at the Screening visits);
- WOMAC (all subscales);
- Patient's Global Assessment of Osteoarthritis;



**NOTE:** Subjects should be thoroughly instructed on completion of Patient's Global Assessment of Osteoarthritis questionnaires, no coaching or other interpretative assistance should be given to subjects during completion of these questionnaires;

- Musculoskeletal physical examination;
- Vital signs after sitting for at least 5 minutes, (blood pressure, and heart rate).
- Orthostatic blood pressure (supine/standing) measurement;
- Review of concomitant medication;
- Rescue medication review;
- Instruction/review of subject compliance with diary assessments and operation of the IRT;
- Confirm with female subjects of child bearing potential that they understand and are willing to follow the contraceptive requirements;
- Adverse Events that occurred after signing the Informed Consent Document (pretreatment Adverse Events);
- Urine pregnancy test for females of childbearing potential (must be negative).

#### **6.4.2. Randomization**

- If still eligible, the subject can be randomized. Randomization will be accomplished through an IRT. The randomization number assigned to the subject will be provided by the system.

#### **6.4.3. Pre-dosing (Day 1)**

Randomized subjects will undergo the following assessments prior to the first dose of investigational product. Some of these may be performed prior to randomization for convenience:

- WPAI:OA;
- EQ-5D-5L;
- Health Care Resource Utilization (HCRU);
- Neurologic exam/Neuropathy Impairment Score;
- Clinical laboratory tests (blood chemistry, hematology);
- Serum and plasma retention samples;

0909077671@08Feb2019 15:51:01 PM  
Pfizer Inc. Internal Use Only  
Confidential  
0909077671@08Feb2019 08:28 (GMT)



- ## 6.6. Week 4

- PFIZER CONFIDENTIAL  
Page 60

- Female subjects of child-bearing potential to be reminded of contraceptive requirements.

## 6.7. Week 8

### 6.7.1. Predosing (Week 8)

- WOMAC (all subscales);
- Patient's Global Assessment of Osteoarthritis;
- EQ-5D-5L;
- Vital signs after sitting for at least 5 minutes, (blood pressure and heart rate);
- Orthostatic blood pressure (supine/standing) measurement;
- Musculoskeletal Physical Examination;
- Neurologic exam/Neuropathy Impairment Score (referral for neurological consult if required);
- Concomitant medication review/update;
- Adverse event review;
- Subject diary entries and compliance review (daily index joint pain score, weekly non-index joint pain assessment and as applicable, daily rescue medication and weekly NSAID use entries);
- Rescue medication compliance review/Dispense;
- Blood samples for PK and PD (NGF) analyses;
- Blood sample for Anti-Drug Antibody assessment;
- Blood and urine samples for biomarkers (CCI [REDACTED] [REDACTED] See [Section 7.6](#));
- Urine pregnancy test for females of childbearing potential (must be negative prior to dosing);
- Female subjects of child-bearing potential to be reminded of contraceptive requirements.

0909077671e08fa28-15510phdMedVAApprovedOn:24-Oct-2019 08:28 (GMT)

### 6.7.2. Dosing (Week 8)

Subjects will receive a single SC injection of blinded investigational product according to the treatment assigned by the IRT system (see [Section 5](#)).

The administration of investigational product will be performed by medical staff and where facilities to handle allergic reactions are available. Should a subject experience symptoms typical of an allergic reaction then investigational product administration should be discontinued immediately and permanently. No other dosage modifications are allowed. Subjects will receive appropriate treatment at the discretion of the investigator.

### 6.7.3. Post-Dosing (Week 8)

Subjects will be observed in clinic for at approximately 1 hour after dosing.

#### **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 (eg, shortness of breath, anaphylaxis, urticaria, angioedema) after leaving the clinic.

### 6.8. Week 12

- WOMAC (all subscales);
- Patient's Global Assessment of Osteoarthritis;
- Vital signs after sitting for at least 5 minutes, (blood pressure and heart rate);
- Orthostatic blood pressure (supine/standing) measurement;
- Musculoskeletal physical examination;
- Neurologic exam/Neuropathy Impairment Score (referral for neurological consult if required);
- Concomitant medication review/update;
- Adverse event review;
- Subject diary entries review and compliance review (daily index joint pain score, weekly non-index joint pain assessment and as applicable, daily rescue medication and weekly NSAID use entries);
- Rescue medication compliance review/Dispense;
- Blood samples for PK and PD (NGF) analyses in a subset of patients;

0909077671e08fa28-15510prtdvmed00n.240fcti-2019 08:28 (GMT)

- Female patients of child-bearing potential to be reminded of contraceptive requirements.

#### **6.9. Week 16 (End of Treatment; Beginning of Safety Follow-Up Period)**

- WOMAC (all subscales);
- Patient's Global Assessment of Osteoarthritis;
- WPAI:OA;
- EQ-5D-5L;
- Weight;
- Vital signs after sitting for at least 5 minutes, (blood pressure and heart rate);
- Orthostatic blood pressure (supine/standing) measurement;
- ECG (12-lead);
- General Physical Examination;
- Musculoskeletal assessment;
- Neurologic exam/Neuropathy Impairment Score (referral for neurological consult if required);
- Concomitant medication review/update;
- Adverse event review;
- Subject diary entries review and compliance review (daily index joint pain score, weekly joint pain assessment, and rescue medication and NSAID use entries if applicable);
- Rescue medication compliance review/Dispense;
- Serum pregnancy test for females of childbearing potential;
- Plasma and serum retention samples);
- Blood samples for PK and PD (NGF) analyses;
- Blood sample for Anti-Drug Antibody assessment;

0909077671908fa28455a10p10Dredfa/episovered00n.24Feb-2019 08:28 (GMT)



- Instruct subject on visit schedule for the Follow-Up Period, including (but not limited to) maintenance of concomitant medication rules and changes to schedule of diary entries via IRT;
- Reminder to female subjects of child-bearing potential to continue with contraceptive requirements.

**6.10. Week 20 (Safety Follow-Up Period Phone Visit)**

- Review/Update of concomitant medication;
- Subject diary entries review and compliance review (weekly joint pain, rescue medication and NSAID use entries);
- Adverse events review;
- Female subjects of child-bearing potential to be reminded of contraceptive requirements.

**6.11. Week 24 (Safety Follow-Up Period Efficacy Visit)**

- WOMAC (all subscales);
- Patient's Global Assessment of Osteoarthritis;
- Survey of Autonomic Symptoms (SAS);
- Health Care Resource Utilization (HCRU);
- Vital signs after sitting for at least 5 minutes, (blood pressure and heart rate);
- Orthostatic blood pressure (supine/standing) measurement;
- Musculoskeletal physical examination;
- Neurologic exam/Neuropathy Impairment Score;
- Subject diary entries review and compliance review (weekly joint pain, rescue medication and NSAID use entries);
- Concomitant medication review/update;
- Rescue medication compliance review/dispense;
- Adverse events review;
- Clinical laboratory tests (blood chemistry, hematology);

0909077671e08f6a28c4e5a10prtdvredflvaipisovered00n.240fcti-2019 08:28 (GMT)

- Blood and urine samples for biomarkers (CCI [REDACTED] [REDACTED] see [Section 7.6](#));

### 6.13. Week 32 (Safety Follow-Up Period Phone Visit)

- Review/Update of concomitant medication;
- Subject diary entries review and compliance review (weekly joint pain scores, rescue medication/acetaminophen and NSAID use);
- Adverse events review.

- Radiographic assessment (x-rays) of both knees, both hips and both shoulders and any other joint for which a radiograph was obtained at the Screening visit or any at risk joint identified during the study period; final study x-ray should be collected as close as possible to the nominal time point of the visit, within a  $\pm 30$  day window,

preferably prior to the Week 40 visit and no more than 14 days after the visit. Refer to [Section 6.16](#) for Early Termination visit description;

- Health Care Resource Utilization (HCRU);
- Survey of Autonomic Symptoms (SAS);
- Musculoskeletal physical examination;
- Vital signs after sitting for at least 5 minutes, (blood pressure and heart rate);
- Orthostatic blood pressure (supine/standing) measurement;
- ECG (12-lead);
- Neurologic exam/Neuropathy Impairment Score (referral for neurological consult if required);
- Concomitant medication review/update;
- Subject diary entries review (weekly joint pain scores, rescue medication/acetaminophen and NSAID use);
- Adverse events review;
- Blood sample for Anti-Drug Antibody assessment.

#### **6.16. Subject Withdrawal/Early Termination Follow-Up Period**

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, behavioral, 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. A subject thought lost to follow-up, must be contacted through a minimum of 3 documented phone call attempts and, if phone calls are unsuccessful, a certified letter sent to 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. Female subjects of child-bearing potential should be reminded to continue contraceptive measures at least 112 days (16 weeks) after the last dose of investigational product.

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

090907767e1e08f6a28c155a10p100redflA4091056Amend001n.240-Final-2019 08:28 (GMT)

collected. Pfizer may retain and continue to use any data collected before such withdrawal of consent.

Subjects discontinuing from treatment (prior to Week 16), either at their request or at the decision of the investigator, will be required to undergo 24 weeks of post-treatment follow-up (as described in [Section 6.16.1](#)). The 24 weeks of follow-up will be obtained through 3 clinic visits and monthly phone calls to yield 24-weeks of post-treatment follow-up, as described in [Section 6.16.1](#). Subjects will be asked to continue to enter pain scores for index joints and provide an assessment of pain in their major, non-index joints (as described in [Section 7.1.1](#)) via IRT, weekly, through the end of the 24-week follow-up period. On a weekly basis during the 24 week safety follow-up period, subjects will also be asked to continue to record rescue medication and NSAID use via IRT.

X-rays of both knees, both shoulders and both hips (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. The remainder of efficacy and safety assessments should be done at the scheduled first visit which is to occur 8 weeks after the last dose of investigational product (as described in 6.16.1.1). 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 investigational product (which corresponds to more than 5 times the elimination half-life of tanezumab) to collect safety and efficacy data (as described in 6.16.1.3). Once the clinic visit 16-weeks after the last administration of investigational product has been completed and final efficacy assessments have been collected, standard of care treatment will 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 investigational product. That visit, (described in 6.16.1.5), includes repeat bilateral shoulder, knee and hip radiographs as well as any additional joint that was imaged at Screening or any joint identified as at risk during the study, providing at least 30 days have elapsed since the last radiographs were obtained. The window for obtaining end of study X-rays is 30 days from the nominal time of the visit. Every effort should be made to have the subject agree to complete the entire 24 week Early Termination Safety Follow-Up described above.

In the event a subject refuses the Early Termination safety follow-up, or chooses to discontinue during the safety follow-up (after Week 16 and through Week 40), a complete early termination visit should be performed. This early termination visit should include all procedures scheduled for the Week 24 and Week 40 visits unless the Week 24 visit has already been completed, in which case only Week 40 procedures will be required. In addition, if the Week 16 visit was not completed prior to termination, a general physical examination, body weight, WPAI:OA and EQ-5D-5L will also be obtained. Subjects will be advised to continue their contraception regimen during a period of 112 days (16 weeks) after the last dose of investigational product.

Subjects entered in the Early Termination Follow-Up period will be able to take acetaminophen daily up to the Early Termination Follow-Up period Visit 2 (which occurs

0909077671e08fa28d55a0p010d7edfa4aprisoverd00n.240fati-2019 08:28 (GMT)

16 weeks after the last dose of investigational product), but will be advised not to exceed 3000 mg per day. Subjects will be requested not to take acetaminophen (or any other analgesic) in the 24 hours that precede clinic visits at which efficacy assessments are collected (Early Termination Follow-Up period Visits 1 and 2, which occur 8 and 16 weeks after the last dose of investigational product, respectively).

#### **6.16.1. Early Termination Follow-Up Period Procedures**

As soon as possible after the decision to withdraw was made and provided 30 days have elapsed since the last set of X-rays were collected:

- Radiographs of all joints for which X-rays were obtained at Screening and other at risk joint identified during the study period.

Procedures to be conducted at the Early Termination Follow-Up period in clinic visits and telephone visits are described in Sections 6.16.1.1, 6.16.1.2, 6.16.1.3, 6.16.1.4, and 6.16.1.5.

##### **6.16.1.1. Early Termination Follow-Up Period Visit 1 (8 weeks after last dose received)**

- WOMAC (all subscales);
- Patient's Global Assessment of Osteoarthritis;
- Survey of Autonomic Symptoms (SAS);
- WPAI:OA;
- EQ-5D-5L;
- Weight;
- Vital signs after sitting for at least 5 minutes, (blood pressure and heart rate);
- Orthostatic blood pressure (supine/standing) measurement;
- ECG (12-lead);
- General physical examination;
- Musculoskeletal physical examination;
- Neurologic exam/Neuropathy Impairment Score (referral for neurological consult if required);
- Review/Update of concomitant medication;
- Assess compliance with IRT and review diary entries (weekly joint pain, rescue medication and NSAID use entries);

0909077671e08f6a28c455a101d0eaf1a4e9isovered00n.240404-2019 08:28 (GMT)

- Adverse events review;
- Dispense rescue medication;
- Serum and plasma retention samples;
- Serum pregnancy test for female subjects of childbearing potential;
- Blood sample for Anti-Drug Antibody assessment;
- Blood samples for PK and PD (NGF) analyses;
- Blood and urine samples for biomarkers (CCI [REDACTED] [REDACTED] See [Section 7.6](#));
- Reminder to female subjects of child-bearing potential to continue with contraceptive requirements.

#### **6.16.1.2. Early Termination Follow-Up Period Phone Visit (12 weeks post last dose)**

- Review/Update of concomitant medication
- Review subject compliance with weekly diary and review entries (weekly joint pain, rescue medication and NSAID use entries);
- Adverse events review;
- Female subjects of child-bearing potential to be reminded of contraceptive requirements.

#### **6.16.1.3. Early Termination Follow-Up Period Visit 2 (16 weeks after last dose received)**

- WOMAC (all subscales);
- Patient's Global Assessment of Osteoarthritis;
- Survey of Autonomic Symptoms (SAS);
- Health Care Resource Utilization (HCRU);
- Musculoskeletal physical examination;
- Neurologic exam/Neuropathy Impairment Score (referral for neurological consult if required);
- Review/Update of concomitant medication;

09090776719081628-11510 prd\med\A\approved\CD\in 24 Feb 2019 08:28 (GMT)



- #### 6.16.1.4. Early Termination Follow-Up Period Phone Visit (20 weeks post last dose)

- #### 6.16.1.5. Early Termination Follow-Up Period Visit 3 (24 Weeks after last dose)

- PFIZER CONFIDENTIAL  
Page 70

- ### 6.16.2. Procedures for Subjects Undergoing Joint Replacement

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 protocol (Study A4091064; provided the subject consents).

- Subjects who have undergone or plan an immediate total knee, hip or shoulder replacement procedure will be discontinued from the treatment period and enter into Study A4091064. At the discontinuation visit, all End of Treatment (Week 16) and Week 24 procedures should be completed (6.9 and 6.11); unless the subject has already completed the Week 16 and Week 24 visits, in which case only the Week 40 visit procedures should be completed ([Section 6.15](#)). In addition, if the Week 16 visit or Week 24 visit was not completed prior to termination, a general physical examination, WPAI:OA, EQ-5D-5L will also be obtained. Applicable Study A4091064 Baseline visit activities should be completed on the same day as the Study A4091056 End of Treatment Visit.



## Index Joint Pain Assessment

- Example of question when the index joint is the knee:

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

- Example of question when the index joint is the hip:

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

### Non-index Joint Pain Assessment

Post-baseline, assessment of pain in the non-index joints will be done weekly by asking subjects if they experienced new or increased pain in non-index major joints via IRT. If a subject responds that he/she has experienced increased pain in a non-index joint, the subject will be asked to rate his/her pain in that joint using a 24-hour recall period on the same 11-point numeric rating scale shown above for the remainder of the study.

### **7.1.2. Rescue Medication and Amount**

Rescue medication use will be collected daily via IRT from the beginning of the Initial Pain Assessment Period to the Week 16 Visit. The dosage strength of the acetaminophen tablets/caplets/capsules will be captured. The subject should note the number of pills (tablets/caplets/capsules) of rescue medication taken during the last 24 hours.

Following the Week 16 visit and up to Week 40 (or during the Early Termination Follow-Up, for subjects who enter that phase of the study), the use of acetaminophen as rescue medication (number of days and maximum amount used in a day) will be reported weekly via IRT.

### **7.1.3. Concomitant NSAID Use**

Use of over-the counter or prescription NSAID will be collected weekly via IRT from the Initial Pain Assessment Period until the Week 40 visit (or through the Early Termination Follow-Up period for subjects who enter this phase of the study). Subjects will 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 additional information, such as the medication name, dosage and reason for use on the 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**

### **7.2.1. Western Ontario and McMaster Universities Osteoarthritis Index**

A copy of the WOMAC<sup>44</sup> Osteoarthritis NRS Index NRS 3.1 English for USA – V5 is presented in Appendix 4. The WOMAC subscales will be recorded by the subjects via IRT at relevant study visits.

#### **7.2.1.1. WOMAC Pain Subscale**

The WOMAC Pain subscale questionnaire is to be completed by the subject at Screening, Baseline (Day 1, prior to administration of investigational product) and Weeks 2, 4, 8 (Day 57, prior to administration of investigational product), 12, 16 (End of Treatment visit), and 24 (Follow-Up Period efficacy visit) or at Early Termination (as described in [Section 6.16](#)).

The WOMAC Pain subscale questionnaire will be completed for the index knee or hip.

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. 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.

0909077671e08f6a28c1e5a10p100MedfVA (approved) On: 24 Feb 2019 08:28 (GMT)





Subjects who have a hip as index joint will answer the following question: “Considering all the ways your osteoarthritis in your hip affects you, how are you doing today?”

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

Subjects will complete the WPAI:OA at Screening and Week 16 (or at early Termination, as described in [Section 6.16](#)).

#### 7.2.4. EuroQol 5 Dimension (EQ-5D-5L)

The EQ-5D-5L™ is a subject completed questionnaire designed to assess the subject's current health and translate that score into an index value or utility score. Health status is described in terms of 5 dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. There are two components to the EQ-5D-5L™: a Health State Profile and an optional visual analog scale (VAS) item. Only the 5 item health state profile will be assessed to calculate a single index value (see Appendix 7). This instrument provides a mechanism for conducting cost-effectiveness and cost-utility analyses.<sup>46</sup>

The utilization of health care resources (eg, doctor office visits, hospitalizations, surgeries or procedures, etc; see Appendix 12) during the 3 months prior to Baseline will be assessed by questionnaire at Baseline (Day 1). In addition, Health Care Resource Utilization will be collected at study visits at Week 24 and at Week 40. Subjects will enter responses using IRT.

### **7.3. Safety Assessments**

Each subject will provide a general medical history as well as a detailed musculoskeletal/joint specific medical history. The information will be recorded on the appropriate CRF(s) at Screening. Information on prior medications (within 30 days of the Screening Visit for non-analgesic medications, any used for pain and other medications for the treatment and relief of symptoms of OA), non-pharmacologic therapies, supplements and concomitant medication use will be collected at Screening and concomitant medication at each scheduled study visit. Information regarding tobacco and alcohol use and dependency will also be collected at Screening.

#### **7.3.1. Physical Examination**

##### **7.3.1.1. General Physical Examination**

Each subject will undergo a general physical examination at Screening and at Week 16, or at Early Termination (as described in [Section 6.16](#)).

##### **7.3.1.2. Musculoskeletal History and Physical Examination**

Each subject will also undergo a musculoskeletal physical examination at Screening, Baseline (Day 1), and at Weeks 2, 4, 8, 12, 16, 24 and 40 (or at Early Termination, as described in [Section 6.16](#)).

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, gout, pseudogout, osteoporosis or osteopenia, joint injuries or other conditions.

At each visit, 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.

##### **7.3.2. Screening Numeric Pain Scale Rating (NRS)**

Average pain in the major joints (shoulders, hips and knees) or any other painful major joint that will be imaged at Screening, will be assessed by the subject at the Screening Visit with an 11-point Numeric Rating Scale (NRS) ranging from zero (no pain) to 10 (worst possible pain) and captured through IRT.

##### **7.3.3. 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:

090907767e08f6a28845510p10vMedfA4p15000000n.24-04-2019 08:28 (GMT)

**Table 3. Blood and Urine tests**

<b>Chemistry</b>	<b>Hematology</b>	<b>Other</b>	<b>Urinalysis</b>
<u>Screening, Baseline and Week 24 (or Early Termination):</u> Sodium, potassium, chloride, bicarbonate, glucose (non fasting), Blood Urea Nitrogen (BUN), creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, cholesterol, triglycerides, gamma glutamyltransferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactic dehydrogenase (LDH), alkaline phosphatase, creatine phosphokinase (CPK), and uric acid	<u>Screening, Baseline, and Week 24 (or Early Termination):</u> Complete blood count with differential	<u>Screening only:</u> HbA1c Hepatitis screen (eg, HBsAg, Anti-HCV), HIV test (HIV Ab screen)  Urine toxicology screen (eg, for opiates, barbiturates, amphetamines, cocaine, propoxyphene, methadone, phencyclidine, and methaqualone).  Serum FSH if applicable  <u>Screening, Week 16 and Week 24 (or early termination Visits 1 and 2):</u> Serum Pregnancy Test  <u>Baseline and Week 8 (Prior to dosing at Dosing Visits):</u> Urine Pregnancy Test  <u>Baseline, Week 16 and Week 24 (or Early Termination Visits 1 and 2):</u> Serum and plasma retention samples	<u>Screening only:</u>  pH, protein, glucose, ketones, blood, bilirubin, nitrite, specific gravity and leukocytes.  Microscopic analysis performed if abnormalities are present on the above components.
Does not include PK, PD (NGF), ADA and biomarkers (refer to sections below for collection details)			

### 7.3.3.1. Blood Tests

Blood tests for clinical laboratory testing (chemistry, hematology) will be performed at Screening, Baseline and Week 24 (or at Early Termination, as described in [Section 6.16](#)). An unscheduled visit(s) may be necessary for follow-up of abnormal test results.

Serum and plasma retention samples will be collected at Baseline, Week 16 and Week 24 or at Early Termination (as described in [Section 6.16](#)).

See [Section 7.3.3.3](#) for sample collected for serum pregnancy test and [Section 7.3.3.4](#) for sample collected for FSH testing.

Blood samples collected for PK, PD (NGF), biomarkers and anti-drug antibody measurements are described in [Sections 7.3.9](#), [7.5](#), and [7.6.1](#)).

### 7.3.3.2. Urinalysis and Urine Toxicology Screen

Urinalysis and urine toxicology screen will be performed at Screening only.

See [Section 7.3.3.3](#) for urine pregnancy test.

Urine samples collected for biomarker analyses are described in [Section 7.6.2](#)).



### 7.3.4. Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure, heart rate) will be collected and recorded throughout the study at Screening, Baseline (Day 1, prior to administration of investigational product), and at Weeks 2, 4, 8 (prior to dosing), 12, 16 (End of Treatment visit), 24 and 40, or at Early Termination visit (as described in [Section 6.16](#)). Vital signs will be collected after the subject has been in a sitting position for at least five minutes at each noted visit.

#### 7.3.4.1. Orthostatic Blood Pressure Measurement

In addition to sitting vital sign measurements, orthostatic blood pressure measurements will be obtained using a standard manual sphygmomanometer at Screening, Baseline (Day 1), and at Weeks 2, 4, 8, 12, 16 (End of Treatment), 24 and 40 (End of Study; or at Early Termination, as described in [Section 6.16](#)). At each of these clinic visits, blood pressure will be assessed in supine and standing positions. Orthostatic blood pressure measurements will be obtained after collection of the sitting vital signs and before any required phlebotomy (and prior to dosing at dosing visits). 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 time points. If the measurements do not meet the criteria for orthostatic (postural) hypotension, no further measurements are needed. If either the 1 minute standing or the 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 and actions that should be taken when orthostatic hypotension criteria are met.

Mean Supine Systolic Blood Pressure	Decrease in Blood Pressure Defining Orthostatic (postural) Hypotension	Actions (for both criteria)
≤150 mmHg	≥20 mmHg systolic <b>or</b> ≥10 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 an adverse event of orthostatic hypotension will be reported.  - Refer to <a href="#">Section 7.4.3</a> for subject management and guidance.
OR >150 mmHg	≥30 mmHg systolic <b>or</b> ≥15 mmHg diastolic	

### 7.3.5. 12-lead Electrocardiogram

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, QTcF, 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 investigational product assignment. In the event a clinically significant ECG abnormality is seen at a visit on an ECG obtained for cause (post-treatment), the investigator should consider evaluation of the subject by a cardiologist.

- Significant bradycardia (heart rate of  $\leq 45$  beats per minute (BPM) on an ECG, exclusionary at Screening).
- Heart rate decrease from Screening of  $\geq 25\%$  with resulting heart rate  $< 60$  BPM.

PFIZER CONFIDENTIAL  
Page 81





For subjects who are identified with a possible or probable joint event (ie, rapidly progressive osteoarthritis, subchondral insufficiency fractures, spontaneous osteonecrosis of the knee (SPONK), primary osteonecrosis or pathological fracture) 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.

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 “**As Low As Reasonably Achievable (ALARA)**, 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	0.024 mSV
Hip	1.9 mSV
Shoulder	0.04 mSV
Total	1.964 mSV

PFIZER CONFIDENTIAL  
Page 83

Neurologic examinations will be performed by a designated physician at Screening, Baseline, and Weeks 2, 4, 8, 12, 16, 24 and 40, (or at Early Termination, as described in [Section 6.16](#)) and the Neuropathy Impairment Score (NIS) will be completed at these time points based on this neurological exam (see Appendix 7). Neurologic examination will assess strength of groups of muscles of the head and neck, upper limbs and lower limbs, deep tendon reflexes and sensation (tactile, vibration, joint position sense and pin prick) of index fingers and great toes in order to complete the NIS. The NIS is a standardized instrument which has been tested in both healthy subjects and subjects with neuropathy and which has been used to evaluate subjects for signs of peripheral neuropathy in clinical trials.<sup>51</sup> Investigators and other designated physicians performing the neurologic evaluations are required to attend a training session for neurological exam in order to apply consistency across sites. The neurological exams must be performed in a controlled and consistent manner and by the same examiner when possible.

- If an adverse event suggestive of new or worsening peripheral neuropathy or an adverse event of abnormal peripheral sensation (eg, allodynia, burning sensation, carpal tunnel syndrome, dysesthesia, hyperesthesia, hyperpathia, hypoesthesia, neuralgia, neuritis, neuropathy peripheral, paresthesia, peripheral sensory neuropathy, sensory disturbance, sensory loss, sciatica, tarsal tunnel syndrome) is reported as: 1) a serious adverse event or 2) an adverse event which has resulted in the subject being withdrawn from the study, or 3) an adverse event ongoing at the end of the subject's participation in the study, or 4) an adverse event of severe intensity.
- A new or worsened clinically significant abnormality on the neurologic exam should be reported as an adverse event and may result in a neurologic evaluation/consult further to the guidance above.
- A neurological adverse event which is non-neuropathic (eg, stroke, seizure) but which the investigator considers medically important should also result in a neurological consultation.

### 7.3.9. Anti-Drug Antibody Testing

PFIZER CONFIDENTIAL  
Page 84

Week 16, ADA will be determined at approximately Weeks 8, 16 and 24 weeks after the last SC dose was administered.

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

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

Samples may be used for further evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical report.

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

#### **7.4. Triggered Events and Subject-Level Stopping Rules**

The following rules will apply to individual subjects at the time of the second injection of SC investigational product.

##### **7.4.1. Dysesthesia/Allodynia**

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

Unresolved dysesthesia/allodynia: Withhold the SC investigational product 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 the second dose of investigational product and will enter the Early Termination Follow-Up Period (see [Section 6.16](#)).

##### **7.4.2. Hypersensitivity or Injection Site Reactions**

If a severe hypersensitivity reaction or severe injection reaction occurs following the first administration of SC investigational product, investigational product should be discontinued immediately and no further administration of SC investigational product will be allowed. Subjects experiencing these types of reactions will enter the Early Termination Follow-Up Period (see [Section 6.16](#)).

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 7.3.4.1](#) will be designated as confirmed orthostatic hypotension episode and should be reported as an adverse event whether or not the subject had accompanying symptoms.

0909077671e08f6a28-15510-phd-Confidential-2019 08:28 (GMT)

Confirmed episodes of orthostatic hypotension: If a confirmed episode of orthostatic hypotension occurs (as defined in [Section 7.3.4.1](#)) it should be reported as an adverse event and the subject should be further evaluated described below to determine below to determine if a neurology or cardiology consultation should be obtained and/or whether further treatment with investigational product should occur. Figure 1 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 investigational product.
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 7.3.4.1](#)) 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 7.3.5](#) for ECG criteria for bradycardia), syncope, orthostatic hypotension (as described above and in boxes C and E of flow diagram Figure 1), 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 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 investigational product 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 treatment (Boxes H and K of flow diagram Figure 1). 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 investigational product; even if a sympathetic autonomic neuropathy has not been confirmed (Boxes J and L of flow diagram Figure 1), and will enter the Early Termination Follow-up period (refer to

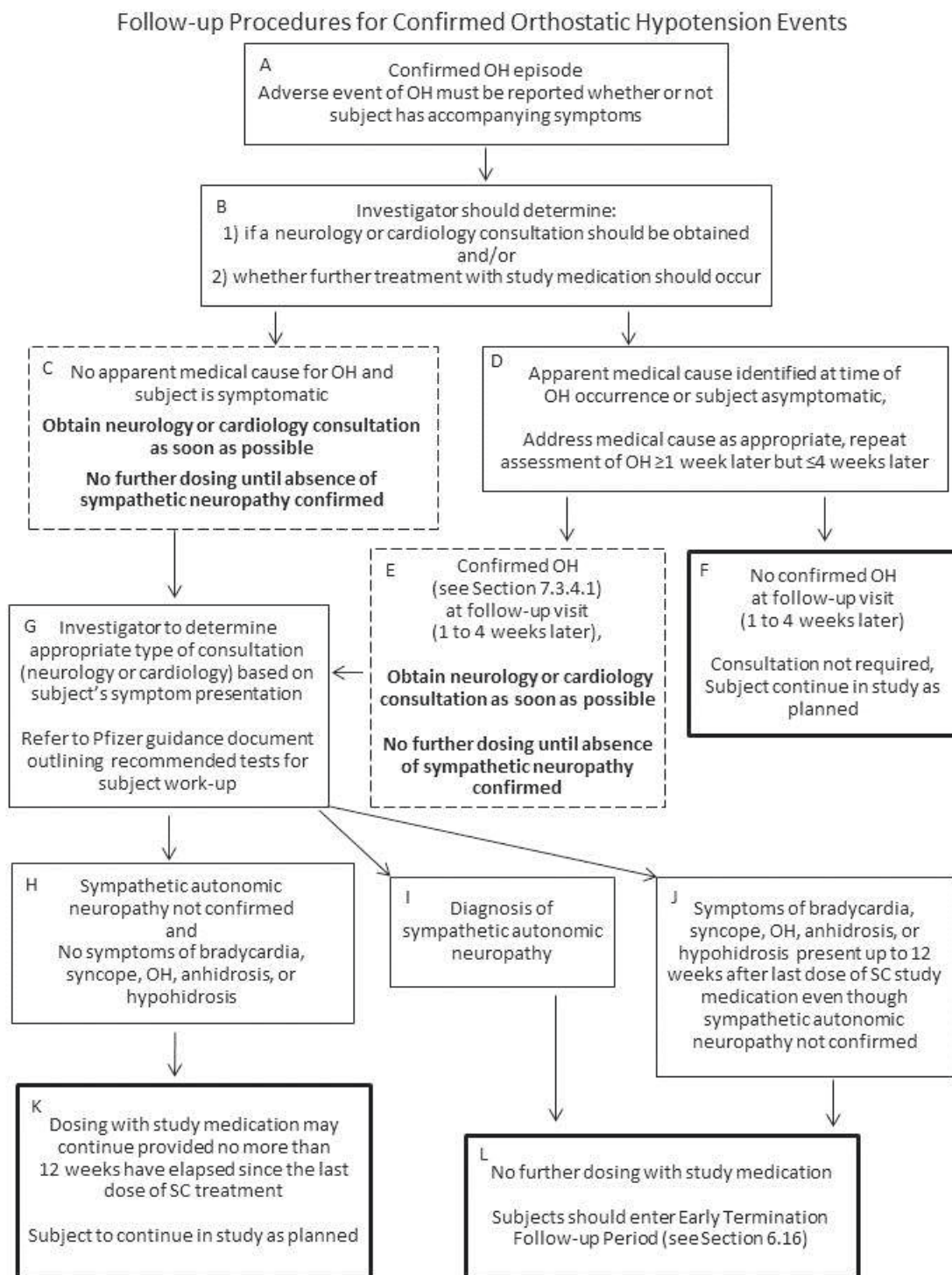
0909077671e08f6a28-11e5-9100-000119f89f3d 24 Feb 2019 08:28 (GMT)

[Section 6.16.1](#)). Subjects found to have a sympathetic autonomic neuropathy (Boxes I and L of flow diagram Figure 1) should not be receive additional investigational product and will enter the Early Termination Follow-up period (refer to [Section 6.16.1](#)).

09090777e71e08fa28c155a0p1h0vcaflva\prison\ee00n.24-0ct-2019 08:28 (GMT)



### Figure 1. Follow-up Procedures for Confirmed Orthostatic Hypotension Events



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

Average daily pain in the index joint will be assessed with an 11-point numeric rating scale (0 to 10) and collected via IRT beginning in the IPAP and through Week 16, followed by weekly assessments during the Follow-Up period. In addition, on a weekly basis beginning at the Initial Pain Assessment Period and through Week 40 of the study, the subject will also be asked if he/she has experienced new or increased pain in a major, non-index joint such as knee, hip or shoulder. If a subject responds that he/she has experienced new or increased pain in a major, non-index 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 (see [Section 7.1](#)) and will continue reporting pain in that joint for the remainder of the study.

Joint pain scores recorded electronically will be monitored by site staff to identify subject 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 radiographically. An earlier evaluation of the subject can be made at the discretion of the investigator.

At each study visit, systematic site review of the WOMAC Pain Scores, 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, fractures or worsening of osteoarthritis symptoms in index or non-index joints will be evaluated by the site personnel. An assessment of the subjects' general health and major joints for any changes in their osteoarthritis status will be carried out.

Musculoskeletal physical exam findings, review of reported musculoskeletal adverse events, and in-clinic efficacy assessments will be recorded on specific case report forms for each study visit.

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 a 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 should be obtained if warranted for diagnostic purposes. If warranted, the subject will be referred to an orthopedic surgeon for evaluation.

Radiology (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.

0909077671@08Feb2019 08:28 (GMT) Pfizer Confidential

#### **7.4.5. Central Reader and Subject-Level Stopping Criteria for Joint Safety Events**

Subjects identified through the measures described above (in [Section 7.4.4](#)) who are determined by the Central Reader to have possible or probable rapidly progressive osteoarthritis, 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 (see [Section 6.16](#)).

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.

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 6.16](#)).

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 9.6.1.3](#).

#### **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. Follow up procedures for these subjects are described in [Section 6.16.2](#). In addition, subjects who undergo total knee, hip or shoulder joint replacement surgery during the study (Treatment Period or Follow up Period) will be followed for 24 weeks after the procedure as part of a separate protocol, provided the subject consents (see [Section 6.17](#)).

### **7.5. Pharmacokinetic (PK) and Pharmacodynamic (PD)**

#### **7.5.1. Plasma for Analysis of Tanezumab**

Blood samples for the assessment of the pharmacokinetics of tanezumab will be collected pre-dose at Baseline (Day 1) and at Weeks 2 (in a subset of subjects), 4 (in a subset of subjects), 8 (pre-dose), 12 (in a subset of subjects), 16, and 24 (or at Early Termination, as described in [Section 6.16](#)). Specifically, if subject terminates prior to Week 16, PK will be determined at approximately 8 and 16 weeks after the last SC dose was administered.

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

Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

09090776719081628-11510 pfdrad1A (approved) 001n. 24 Feb 2019 08:28 (GMT)

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

Blood samples for the assessment of CCI NGF (if assay is available) concentrations will be collected pre-dose at Baseline (Day 1) and at Weeks 2 (in a subset of subjects), 4 (in a subset of subjects), 8 (pre-dose), 12 (in a subset of subjects), 16, and 24 (or at Early Termination, as described in [Section 6.16](#)). Specifically, if subject terminates prior to Week 16, NGF will be determined at approximately 8 and 16 weeks after the last SC dose was administered.

Country	CCl
China	100%
USA	99%
Germany	98%
France	97%
Japan	96%
UK	95%
India	94%
South Korea	93%
Canada	92%
Italy	91%
Spain	90%
Sweden	89%
Australia	88%
Brazil	87%
South Africa	86%
Argentina	85%
Mexico	84%
Colombia	83%
Peru	82%
Venezuela	81%
Ecuador	80%
Bolivia	79%
Paraguay	78%
Uruguay	77%
Chile	76%
Costa Rica	75%
Panama	74%
Dominican Republic	73%
Honduras	72%
Nicaragua	71%
Guatemala	70%
El Salvador	69%
Haiti	68%
Dominican Republic	67%
Jamaica	66%
Trinidad and Tobago	65%
Suriname	64%
Guayana Francesa	63%
Aruba	62%
Curaçao	61%
Bonaire	60%
San Pedro y San Pablo	59%
San Juan	58%
San Vicente y las Grenadinas	57%
Barbados	56%
Antigua y Barbuda	55%
Guayana Francesa	54%
Francia	53%
Reino Unido	52%
Países Bajos	51%
Italia	50%
Francia	49%
Reino Unido	48%
Países Bajos	47%
Italia	46%
Francia	45%
Reino Unido	44%
Países Bajos	43%
Italia	42%
Francia	41%
Reino Unido	40%
Países Bajos	39%
Italia	38%
Francia	37%
Reino Unido	36%
Países Bajos	35%
Italia	34%
Francia	33%
Reino Unido	32%
Países Bajos	31%
Italia	30%
Francia	29%
Reino Unido	28%
Países Bajos	27%
Italia	26%
Francia	25%
Reino Unido	24%
Países Bajos	23%
Italia	22%
Francia	21%
Reino Unido	20%
Países Bajos	19%
Italia	18%
Francia	17%
Reino Unido	16%
Países Bajos	15%
Italia	14%
Francia	13%
Reino Unido	12%
Países Bajos	11%
Italia	10%
Francia	9%
Reino Unido	8%
Países Bajos	7%
Italia	6%
Francia	5%
Reino Unido	4%
Países Bajos	3%
Italia	2%
Francia	1%
Reino Unido	0%

Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

NGF samples may be used for further evaluation of the bioanalytical methods used for measuring NGF. These data will be used for internal exploratory purposes and will not be included in the clinical report.

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

### 7.6.1. Serum Biomarkers

Blood samples for the assessment of biomarkers that can be modulated by the osteoarthritis condition will be collected pre-dose at Baseline (Day 1), at Week 8 (pre-dose) and at Week 24 or Early Termination, as described in [Section 6.16](#). Specifically, if subject terminates prior to Week 16, serum biomarkers will be determined at approximately 8 weeks after the last SC dose was administered and at approximately 16 weeks after the last SC dose was administered.

CCI

CCI

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

Samples will be analyzed using validated analytical methods in compliance with Pfizer standard operating procedures.

Biomarker samples may be used for further evaluation of biomarkers other than the ones listed that could improve the understanding of the safety and efficacy profile of tanezumab. These data will be used for internal exploratory purposes and will not be included in the clinical report.

The shipment address will be provided to the investigator site prior to initiation of the study.

#### 7.6.2. Urine Biomarkers

Urine samples for the assessment of CCI will be collected pre-dose at Baseline (Day 1), Week 8 (pre-dose) and at Week 24 or Early Termination, as described in [Section 6.16](#). Specifically, if subject terminates prior to Week 16, urine biomarkers will be determined at approximately 8 weeks after the last SC dose was administered and at approximately 16 weeks after the last SC dose was administered.

CCI

Sites will provide collection containers and storage instructions for subjects doing home collection.

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

0909077671e08f6a28c1e5510p100redflVA (approved) 000n. 24 Oct-2019 08:28 (GMT)



Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

Biomarker samples may be used for further evaluation of biomarkers other than the ones listed that could improve the understanding of the safety and efficacy profile of tanezumab. These data will be used for internal exploratory purposes and will not be included in the clinical report.

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

## **7.7. Banked Biospecimens**

### **7.7.1. Markers of Drug Response**

Studying the variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomic/biomarker research. Comparing the deoxyribonucleic acid (DNA), ribonucleic acid (RNA), protein, and metabolite variation patterns of subjects who respond well and those who respond poorly to treatment may help to better define the most appropriate group of subjects in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/biomarker analyses and retaining them in the Pfizer BioBank makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study.

Providing these biospecimens is a required study activity for study sites and subjects, unless prohibited as such by local regulations or ethics committee decision.

To protect subjects' confidentiality, the banked biospecimens and data generated from them will be coded with the subject's study identification (ID) number. Samples will be kept in a facility accessible only by swiping a badge. Data will be stored on password-protected computer systems. The key between the code and the subject's personal identifiers will be held at the study site; the researchers using the biospecimens and data generated from them will not have access to the key nor any personally identifying information. Biospecimens will only be used only for the purposes described here and in the informed consent document/subject information sheet; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored indefinitely to allow for future research on the topics described here, including research conducted during the lengthy drug development process and also post-marketing research. Subjects can withdraw their consent for the use of their biospecimens at any time by making a request to the investigator, in which event any remaining biospecimen will be destroyed; data already generated from the biospecimens will continue to be stored to protect the integrity of existing analyses. It is very unlikely that results generated from the biospecimens will have any clinical, diagnostic, or therapeutic implications for the individual study participants. Subjects are notified in the informed consent document/subject information sheet that their results will not be given to them,

0909077619081612019082808:28 (GMT)



unless required by local laws or regulations, in which case results will be returned via the investigator. Results will not be provided to family members or other physicians; nor will they be recorded in the subject's medical record. There is no intention to contact subjects after completion of the clinical study.

A 4 mL blood biospecimen **Prep D1 (K<sub>2</sub>ethylenediaminetetraacetic acid (EDTA) whole blood collection optimized for DNA analysis)** will be collected at the Baseline visit to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. For example, putative safety biomarkers, drug metabolizing enzyme genes, drug transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.

The banked biospecimen will be collected from all subjects unless prohibited by local regulations or ethics committee decision. Detailed collection, processing, storage and shipment instructions are provided in the central laboratory manual.

It is possible that the use of these biospecimens may result in commercially viable products. Subjects will be advised in the informed consent document/subject information sheet that they will not be compensated in this event.

#### 7.7.2. Additional Research

Unless prohibited by local regulations or ethics committee decision, subjects will be asked to indicate on the consent form whether they will allow the banked biospecimens to also be used for the following research:

- Investigations of the disease under study in the clinical study, and related conditions.
- Biospecimens may be used as controls. This includes use in case-control studies of diseases for which Pfizer is researching drug therapies; use in characterizing the natural variation amongst people in genes, RNA, proteins, and metabolites; and use in developing new technologies related to pharmacogenomics/biomarkers.

Subjects need not provide additional biospecimens for the uses described in [Section 7.7.2](#); the biospecimens specified in the Markers of Drug Response [Section 7.7.1](#) will be used. Subjects may still participate in the clinical study if they elect not to allow their banked biospecimens to be used for the additional purposes described in this Section.

### 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 a

09090775/19081628-15530 pfdrd1A (approved) 001n. 24 Feb 2019 08:28 (GMT)

As part of ongoing safety reviews conducted by the Sponsor, any non-serious 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.

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 product if the subject refuses the protocol defined Follow-Up period.

AEs (serious and non-serious) should be recorded on the CRF from the time the subject has taken at least 1 dose of investigational product through the subject's last visit.

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:

- PFIZER CONFIDENTIAL  
Page 95

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 CRF which is a specific version of the 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 adverse event, as determined by the investigator, the medication error should be captured on the medication error version of the 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

0909077671e08fa28455a0p10MedfAApprovedOn:29-Oct-2019 08:28 (GMT)



- 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  $\geq 3$  times the upper limit of normal (X ULN) concurrent with a total bilirubin value  $\geq 2$  X ULN with no evidence of hemolysis and an alkaline phosphatase value  $\leq 2$  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 pre-existing AST or ALT baseline values above the normal range: AST or ALT values  $\geq 2$  times the baseline values and  $\geq 3$  X ULN, or  $\geq 8$  X ULN (whichever is smaller).

0909077671e08fa28455a10phdVedfVAepisovered00n.24-0ct-2019 08:28 (GMT)

#### Concurrent with

- For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin increased from baseline by an amount of at least 1 time the upper limit of normal or if the value reaches  $\geq 3$  times the upper limit of normal (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;

09090777/19081628-11510 pfdr/medflw/Approved On: 29 Oct 2019 08:28 (GMT)



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

- Diagnostic and therapeutic non-invasive 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.

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:

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 non-serious); 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 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;

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).

2. A male subject 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 an SAE Report Form and 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).

0909077671e08f6a28465a10p100redflvaiprisonred00n.240fatti-2019 08:28 (GMT)

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.

- 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 serious adverse events when the investigator assesses the infant death as related or possibly related to the exposure to investigational product.

### 8.10.1. Additional Postnatal Development Follow-Up

## 8.11. Occupational Exposure

PFIZER CONFIDENTIAL  
Page 102

## 8.12. Withdrawal Due to Adverse Events (See Also [Section 6.16 Subject Withdrawal](#))

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

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

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.

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 timeframe 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/her first awareness of the AE.

PFIZER CONFIDENTIAL  
Page 103

### 8.14.2. Non-Serious Adverse Event Reporting Requirements

### 8.14.3. Medical Device Complaint Reporting Requirements

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

Adverse event 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, 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

A sample size of approximately 230 subjects per treatment group is needed to provide approximately 90% power to achieve statistical significance (at the 5% two-sided level) for the two comparisons of tanezumab 2.5 and 2.5/5 mg SC versus placebo, over all three co-primary endpoints. The total sample size will be approximately 690 subjects.

The assumed treatment differences for this calculation comes from a combined analysis of Studies A4091011 and A4091014, using an ANCOVA model for the change from Baseline to Week 16 with Baseline Observation Carried Forward (BOCF) used for missing data. Under this model the difference between tanezumab 2.5 mg and placebo were approximately -1.0 for WOMAC Pain and Physical Function subscales, and -0.32 for the Patient's Global Assessment of Osteoarthritis. The within-group standard deviations were 2.73, 2.58 and 0.92 for WOMAC Pain, WOMAC Physical Function and Patient's Global Assessment of Osteoarthritis, respectively. The correlation of the change from Baseline to Week 16 value for WOMAC Pain versus Physical Function was 0.93. The correlations between Patient's Global Assessment of Osteoarthritis and WOMAC Pain and Physical Function were approximately 0.68.

Using the treatment differences, variability and correlations given above, the sample size of 230 subjects per group would give 90% power to show significant treatment differences using the two-sided 5% significance, for the two tanezumab versus placebo comparisons over all three co-primary efficacy endpoints.

## 9.2. Efficacy Analysis

### 9.2.1. Analysis of Primary Endpoint

The primary efficacy population will be the ITT population, defined as all randomized subjects who received SC investigational product (either tanezumab or matching placebo). The primary analysis will use multiple imputation methods for missing data at Week 16. Details of the multiple imputation procedure are given below. All treatment comparisons will use the two-sided 5% significance level.

The co-primary efficacy endpoints will be analyzed using an ANCOVA model, with model terms for Baseline score, Baseline diary average pain, index joint (knee or hip), Kellgren-Lawrence grade, and treatment group, and study site as a random effect. The assessment of significance for the tanezumab SC versus placebo treatment contrasts will use a step-down testing strategy within each of the co-primary efficacy endpoints defined as first testing tanezumab 2.5/5 mg versus placebo, and if statistically significant ( $p \leq 0.05$ ) to then test tanezumab 2.5 mg versus placebo. Finally, a tanezumab treatment group is declared as superior to placebo if the corresponding treatment contrast is significant over all three co-primary endpoints. This testing procedure will maintain the Type I error to 5% or less within each of the co-primary efficacy endpoints, and to less than 5% for all three co-primary efficacy endpoints. An additional (main effects ANCOVA) analysis for each of the co-primary efficacy endpoints will use a per-protocol analysis set, which will exclude subjects who are major protocol deviators.

The primary analysis of the co-primary endpoints 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. For subjects with missing data due to discontinuation prior to Week 16 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 all treatment groups) of

090907761e08f6a28d5e5f0p10d7edf1A4091056v000n.240.Final-2019 08:28 (GMT)





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

The change from Baseline in the Patient's Global Assessment of Osteoarthritis to Weeks 2, 4, 8, 12 and 16 will also be analyzed using Cochran-Mantel-Haenszel (CMH) test, stratified by the combinations of the two stratification factors. Changes by each level of improvement will be summarized. For this analysis imputation for missing data will used mixed BOCF/LOCF, as well as BOCF and LOCF separately. If there are too few subjects in any stratification combination group (defined as <15 subjects in any stratification factor) then an unstratified test will be performed.

The incidence and number of days of use of rescue medication, will be analyzed for Weeks 2, 4, 8, 12, 16 and 24 and the amount of rescue medication use per week will be analyzed for Weeks 2, 4, 8, 12, and 16. The incidence of use of rescue medication will be analyzed using logistic regression for binary data, with model terms for Baseline WOMAC Pain subscale score, Baseline diary average pain, index joint, Kellgren-Lawrence grade, and treatment group. The number of days and amount of rescue medication (mg dosage of acetaminophen) will be analyzed using the Negative Binomial model, with model terms of Baseline WOMAC Pain subscale score, Baseline diary average pain score, index joint, Kellgren-Lawrence grade, and treatment group. Estimated levels of rescue medication use will be shown for each treatment group, and the ratio (with 95% CI) for comparisons versus placebo will be shown. Imputation for missing rescue medication data will use LOCF only.

The incidence of and time to withdrawal due to lack of efficacy will also be analyzed for discontinuation up to Week 16 (end of treatment period). The time to discontinuation will be analyzed using the log-rank test, with Kaplan-Meier estimates of the time to discontinuation shown for selected percentiles, dependent on the level of discontinuation. The expectation is that these would be the 1<sup>st</sup>, 2<sup>nd</sup>, 5<sup>th</sup>, 10<sup>th</sup> and 25<sup>th</sup> percentiles. Other percentiles may be shown if the level of discontinuation due to lack of efficacy as calculated using Kaplan-Meier procedure is sufficiently large. The analysis of the incidence of discontinuation due to lack of efficacy will be made using logistic regression for binary data, with model terms for Baseline WOMAC Pain subscale score, Baseline diary average pain score, index joint, Kellgren-Lawrence grade, and treatment group.

Cumulative WOMAC Pain response and WOMAC Physical Function at Week 16 using response definitions from a reduction of >0% to =100% (in steps of 10%) will be summarized, using mixed BOCF/LOCF (as described above), and also LOCF and BOCF imputation for WOMAC Pain and WOMAC physical function. Imputation with BOCF for subjects with missing data at that timepoint will lead to the subjects being assessed as non-responders for the response endpoint.

A table showing number and percentage of subjects will summarize the response for each dimension (item) for the EQ-5D-5L™ at Baseline and Week 8 and Week 16. These summary tables will be shown by treatment group. In addition, for each treatment and for each time point assessed, descriptive statistics (mean, standard deviations, median, number of

0909077671e08fa28-15510 p110 d11a1e150veed00n.240-12019 08:28 (GMT)

The HCRU data will be reported as outlined in the SAP.

All endpoints up to Week 24 will be summarized (where available), and endpoints up to Week 16 will be analyzed.

### 9.3. Safety Analysis

Selected adverse events of interest and common adverse events will be summarized using Risk Differences between each tanezumab group and placebo, together with 95% confidence interval, using exact methods. In addition, significance testing will be performed for tanezumab versus placebo comparisons using exact methods for the adverse events of interest. There will be no multiplicity adjustment for these significance tests.

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 (See [Section 9.6](#)).

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

The Survey of Autonomic Symptoms (SAS) scores will be summarized by treatment group for the total number of symptoms reported and total impact score. The summary will be shown by visit, and for the change from Baseline.

The NIS is the sum of scores over all 37 items from both the Left and Right side. The change from baseline to each post-baseline visit in the NIS (using LOCF for missing data), and to both the Last and Worst change from Baseline (over all post-Baseline visits) will be summarized, and analyzed using Cochran-Mantel-Haenszel test. The NIS data, the neurological consultation data and the conclusion from neurological examination data will be reported.

The neurological consultation data will be summarized all subjects, and for subjects with adverse events of abnormal peripheral sensation, which are described in the adverse event section above. The “conclusion from the neurological examination” data will be summarized for each timepoint, and then a summary of the final assessment over all neurological examinations for each subject.

The incidence of subjects with any of the joint safety adjudication outcomes of rapidly progressive osteoarthritis (type 1 and type 2), subchondral insufficiency fracture (or SPONK), primary osteonecrosis, or pathological fracture, and for occurrence of total joint replacement will be shown by number of subjects treated and years of exposure (treatment plus follow up periods), for individual treatment groups and differences between tanezumab treatment groups and the placebo treatment group.

### **9.3.1. Anti-Tanezumab Antibodies (ADA)**

The following assessments of ADA formation will be made:

- For each tanezumab dose arm, a listing of anti-drug antibody test results sorted by subject, dose and nominal time post-dose. The listing of results will also include the actual times post-dose.
- For each tanezumab dose arm, the proportion of subjects who develop anti-tanezumab will be summarized for each dose.
- Individual subjects with positive ADA results will be evaluated for potential ADA impact on the individual’s PK, efficacy and safety profile.

0909077671@08Feb2019 08:28 (GMT)  
Pfizer Confidential  
Protocol A4091056  
Final Protocol Amendment 1, 23 September 2015





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.

The external DMC will be provided with a blinded summary of the Adjudication Committee's review of events after each review meeting.

#### **9.6. Data Monitoring Committee**

This study will use an external data monitoring committee (E-DMC).

An independent, E-DMC has been reinstituted 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.

The 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 which 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.

0909077571@081a28-11510 pfdrivedata\approved\0001240401-2019 08:28 (GMT)



### 9.6.1. Protocol-Level Rules for Dosing Suspension/Safety Assessment

#### 9.6.1.1. 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);
- Peripheral neuropathy confirmed with objective findings such as treatment-emergent abnormalities on neurologic examination, nerve conduction abnormalities or biopsy findings consistent with peripheral neuropathy.
- One of the events related to sympathetic dysfunction (orthostatic hypotension, bradycardia, syncope, anhidrosis, or hypohidrosis).

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.

If the protocol-based stopping rule is triggered, the E-DMC will consider the implications of this action on a program-level basis and formulate a recommendation whether it is safe to continue dosing (for some or all treatment groups) in other ongoing tanezumab clinical studies. Decisions regarding stopping treatment in other ongoing tanezumab clinical studies will be made by the Sponsor in consultation with the E-DMC.

Factors that may be considered in making this decision in relation to serious adverse events or adjudicated clinically significant adverse events include:

0909077571e08fa28155a10p1tdvaf1A4091056Amend001n.240.Final-2019 08:28 (GMT)

- Consideration of relationship of investigational product to the adverse event;
- Consideration of whether similar adverse events are occurring in other tanezumab studies with similar subject populations;
- Dosage of tanezumab (2.5 mg or 5 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 and/or co-morbidities;
- Duration of therapy (0-6 months, 6-12 months).

#### 9.6.1.2. 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 osteoarthritis and chronic low back pain studies, dosing will be temporarily suspended in all studies until the relationship to investigational product is established for the given events which were consistent with Hy's Law. 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 tanezumab osteoarthritis and chronic low back pain program may be stopped. The E-DMC will determine whether the dosing suspension should be triggered. Subsequently the E-DMC will formulate a recommendation whether all studies should be permanently terminated. Decisions regarding permanently stopping treatment and terminating studies will be made by the Sponsor in consultation with the E-DMC.

#### 9.6.1.3. 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 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.

CCI  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]

CCI [REDACTED] 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

Pfizer or its agent will conduct periodic monitoring visits during study conduct 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)/Independent Ethics Committee (IEC), 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

090907761e08fa28455a0p1d1edfa4aprisoverd00n.129-fc01-2019 08:28 (GMT)



## 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 & 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 on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, address, 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's personal data consistent with applicable privacy laws.

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

The informed consent document(s) used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/IEC before use, and available for inspection.

The investigator must ensure that each study subject, or his/her legal representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's legally acceptable representative, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

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

#### **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 which 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 sufficient subjects have been recruited and completed the study as stated in the regulatory application (ie, Clinical Trial Application (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, or 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.

0909077571@08Feb2019 08:28 (GMT)



## 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](http://www.clinicaltrials.gov) (ClinicalTrials.gov), [www.pfizer.com](http://www.pfizer.com), and/or the the European Clinical Trials Database (EudraCT), and/or [www.pfizer.com](http://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](http://www.clinicaltrials.gov)

Pfizer posts clinical trial US Basic Results on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) for 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 pre-specified protocol or was terminated.

[EudraCT](http://www.eudra-ct.eu)

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](http://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](http://www.pfizer.com) for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted on [www.clinicaltrials.gov](http://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 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

0909077671e08f6a28-11e5-b101-000000000000n.24-Conf-2019 08:28 (GMT)

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, investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

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.

0909077671e08fa288455a0p100readf1A (approved on 24 Oct-2019 08:28 (GMT))

## 16. REFERENCES

1. Pfizer. TANEZUMAB ARTHRITIS ADVISORY COMMITTEE BRIEFING DOCUMENT. February 8, 2012; In; 2012.  
URL:[http://www.fda.gov/AdvisoryCommittees/Calendar/ucm286556.htm?utm\\_source=fdaSearch&utm\\_medium=website&utm\\_term=March 12, 2012&utm\\_content=1](http://www.fda.gov/AdvisoryCommittees/Calendar/ucm286556.htm?utm_source=fdaSearch&utm_medium=website&utm_term=March 12, 2012&utm_content=1). Access Date: April 4, 2012.
2. Hertz S, Fields E. Addendum to the Background Package for the March 12, 2012, AAC Meeting, Regarding the Agency Adjudication of Cases of Joint Replacements Occurring in Clinical Trials of Anti-NGF Agents. In; March 2, 2012.  
URL:<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/ucm295201.htm>. Access date: April 4, 2012.
3. Rappaport BA. FOOD AND DRUG ADMINISTRATION Center for Drug Evaluation and Research: Background Materials. February 13, 2012. URL:<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/ucm295201.htm>. Access date: April 4, 2012.
4. Bennett DLH, McMahon SB, Rattray M, Shelton D. Nerve growth factor and sensory nerve function. In "Pain and Neurogenic Inflammation", eds. SD Brain and PK Moore. Birkhauser, Basel. 1999.
5. Woolf CJ, Safieh-Garabedian B, Ma QP, Crilly P, Winter J. Nerve growth factor contributes to the generation of inflammatory sensory hypersensitivity. *Neuroscience* 1994; 62:327-31.
6. McMahon SB, Bennett DLH, Priestley JV, Shelton DL. The biological effects of endogenous nerve growth factor on adult sensory neurons revealed by a trkA IgG fusion molecule. *Nature Med* 1995; 1:774-780.
7. Safieh-Garabedian B, Poole S, Allchorne A, Winter J, Woolf CJ. Contribution of interleukin 1 beta to the inflammation induced increase in nerve growth factor levels and inflammatory hyperalgesia. *Br J Pharmacol* 1995; 115:1265-1275.
8. Woolf CJ, Allchorne B, Safieh-Garabedian B, Poole S. Cytokines, nerve growth factor and inflammatory hyperalgesia: the contribution of tumor necrosis factor  $\alpha$ . *Br J Pharmacol* 1997; 121:417-424.
9. Armour KL, Clark MR, Hadley AG, Williamson LM. Recombinant human IgG molecules lacking Fc gamma receptor I binding and monocyte triggering activities. *Eur J Immunol* 1999; 29(8):2613-2624.
10. Armour KL, van de Winkel JG, Williamson LM, Clark MR. Differential binding to human Fc gamma RIIa and Fc gamma RIIb receptors by human IgG wild type and mutant antibodies. *Mol Immunol* 2003; 40(9):585-593.

0909077571@08Feb2019 08:28 (GMT)

11. Tanezumab Investigator's Brochure.
12. Bellamy N, Buchanan WW. A preliminary evaluation of the dimensionality and clinical importance of pain and disability in osteoarthritis of the hip and knee. *Clin Rheum* 1986; 5:231-241.
13. Pfizer Data on File A4091011 CSR approved 9 May 2011.
14. Pfizer Data on File A4091014 CSR approved 1 Aug 2011.
15. Pfizer Data on File A4091015 CSR approved 1 Aug 2011.
16. Pfizer Data on File A4091018 CSR approved 5 Aug 2011.
17. Pham T, van der Heijde D, et al. OMERACT-OARSI Initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. *Osteoarthritis and Cartilage* 2004;12:389-99.
18. Pfizer Data on File A4091030 CSR approved 18 Jan 2012.
19. Pfizer Data on File A4091025 CSR approved 12 Dec 2011.
20. Pfizer Data on File A4091027 CSR approved 01 Feb 2012.
21. Pfizer Data on File A4091043 CSR approved 03 Feb 2011.
22. Castro M. Placebo versus Best-Available-Therapy Control Group in Clinical Trials for Pharmacologic Therapies. Which Is Better? *Proc Am Thorac Soc* Vol 4. pp 570–573, 2007.
23. Rosenberg ZS, Shankman S, Steiner GC, et al. Rapid Destructive Osteoarthritis: Clinical, Radiographic and Pathologic Features. *Radiology* 1992;182:213-216.
24. Dougados M, Guegen A, Nguyen M, et al. Radiographic Features Predictive of Radiographic Progression of Hip Osteoarthritis. *Rev Rheum Engl ed.* 1997;64:795-803.
25. Lequesne M, Amouroux J. Rapidly Destructive Osteoarthritis of the Hip. *La Presse Medicale* 1970;78:1435-1439.
26. Irwin LR, Robert JA. Rapidly Progressive Osteoarthrosis of the Hip. *J Arthroplasty* 1998;13:642-646.
27. Batra S, Batra M, McMurtrie A, et al. Rapidly Destructive Osteoarthritis of the Hip Joint: A Case Series. *J Orthop Surg Res* 2008;3:3.
28. Boutry N, Paul C, Leroy X, et al. Rapidly Destructive Osteoarthritis of the Hip: MR Imaging Findings. *Am J Roentgenol* 2002;179:657-663.

- PFIZER CONFIDENTIAL  
Page 122

- PFIZER CONFIDENTIAL  
Page 123





## **Appendix 2. 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;<sup>54</sup> a sixth category was later added (<http://www.asahq.org/Home/For-Members/Clinical-Information/ASA-Physical-Status-Classification-System>).

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 patients whose organs are being removed for donor purposes.

0909077671e08fa288455a0p1h0vradf1A\aprisovered00n.124-For-2019 08:28 (GMT)

### Appendix 3. Half-Lives of Prohibited Prior and Concomitant Medications

#### Half-Lives of NSAIDs and Other Analgesics

Use of any analgesic except acetaminophen is prohibited throughout the study, beginning 48 hours prior to the start of the Initial Pain Assessment Period or at the period of time prior to the start of the Initial Pain Assessment Period that is at least 5 times the half-life of the particular analgesic used, whichever is greater. Note that a stable regimen of aspirin taken for cardiac prophylaxis at a dose of  $\leq 325$  mg/day is permitted throughout the study.

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

<b>HALF-LIVES OF NSAIDs AND OTHER ANALGESICS</b>		
<b>Analgesic</b>	<b>Half-life (hours)</b>	<b>Minimum Washout Period</b>
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 gels	1.9	2 days
Diclofenac/misoprostol	2.4-9.0	2 days
Diflunisal	13.0	3 days
Dipyrrone	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
Hydromorphone	3.0	2 days
Ibuprofen	2.1	2 days
Indomethacin	4.6	2 days
Ketoprofen	1.8	2 days
Ketorolac	4.0-9.0	2 days
Lidocaine patch or EMLA (lidocaine/prilocaine)	2.0	2 days
Meclofenamate	2.0-4.0	2 days
Mefenamic acid	2.0	2 days

0909077671e08f6a28-1e5a10pr010red000n.240.Fatt-2019 08:28 (GMT)

<b>HALF-LIVES OF NSAIDs AND OTHER ANALGESICS</b>		
Meloxicam	16.0 to 20.0	5 days
Meperidine	3.7	2 days
Mexiletine	6.0-17.0	4 days
Morphine	2.0	2 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
Oxymorphone	7.3-9.4	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
Tapentadol	4	2 days
Tenoxicam	60.0	13 days
Tiaprofenic acid	3.0	2 days
Tolmetin	1.0	2 days
Tramadol	5.9	2 days

**Corticosteroids** The following use of oral or intramuscular corticosteroids is prohibited through Week 24) within 30 days prior to the Initial Pain Assessment Period or, 2) at the period of time prior to the start of the Initial Pain Assessment Period that is at least 5 times the half-life of the particular corticosteroid used, whichever is greater or, 3) the anticipated need to start such during the study. Intra-articular injection of corticosteroids within 12 weeks to the index joint or 30 days to any other joint prior to the Initial Pain Assessment Period is PROHIBITED. Topical, inhaled and intranasal corticosteroids are PERMITTED.

<b>Corticosteroids</b>	
Generic	Brand
betamethasone	Celestone, Soluspan
Cortisone	
dexamethasone	Decadron, Dexacort, Turbinaire
fludrocortisone	Florinet
hydrocortisone	A-hydroCort, Cortef, Hydrocortone, Solu-Cortef
methylprednisolone	Medrol, Solu-Medrol
Prednisolone	Orapred, Prelone
Prednisone	Cortan, Deltasone, Medicorten

## Hyaluronic Acid

Intra-articular hyaluronic acid injection to the index knee is prohibited within 30 days (or within 18 weeks for long-acting formulations such as Synvisc) of the Initial Pain Assessment Period and throughout the study.

## Biologicals

Use of biologicals is prohibited within 3 months of the Initial Pain Assessment Period and during the study.

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.

<b>TNF<math>\alpha</math> Inhibitors</b>	
<b>Generic</b>	<b>Brand</b>
Adalimumab	Humira
Etanercept	Enbrel
Infliximab	Remicade

Use of live attenuated vaccines (with the exception of Flumist<sup>®</sup> Influenza Virus Vaccine Live, Intranasal or other inhaled live attenuated influenza vaccines and Pneumovax) is prohibited within 3 months of Initial Pain Assessment Period and during the study.

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.

0909077671e08fa28d155a0p1tdvradflva (approved) on 24 Oct 2019 08:28 (GMT)

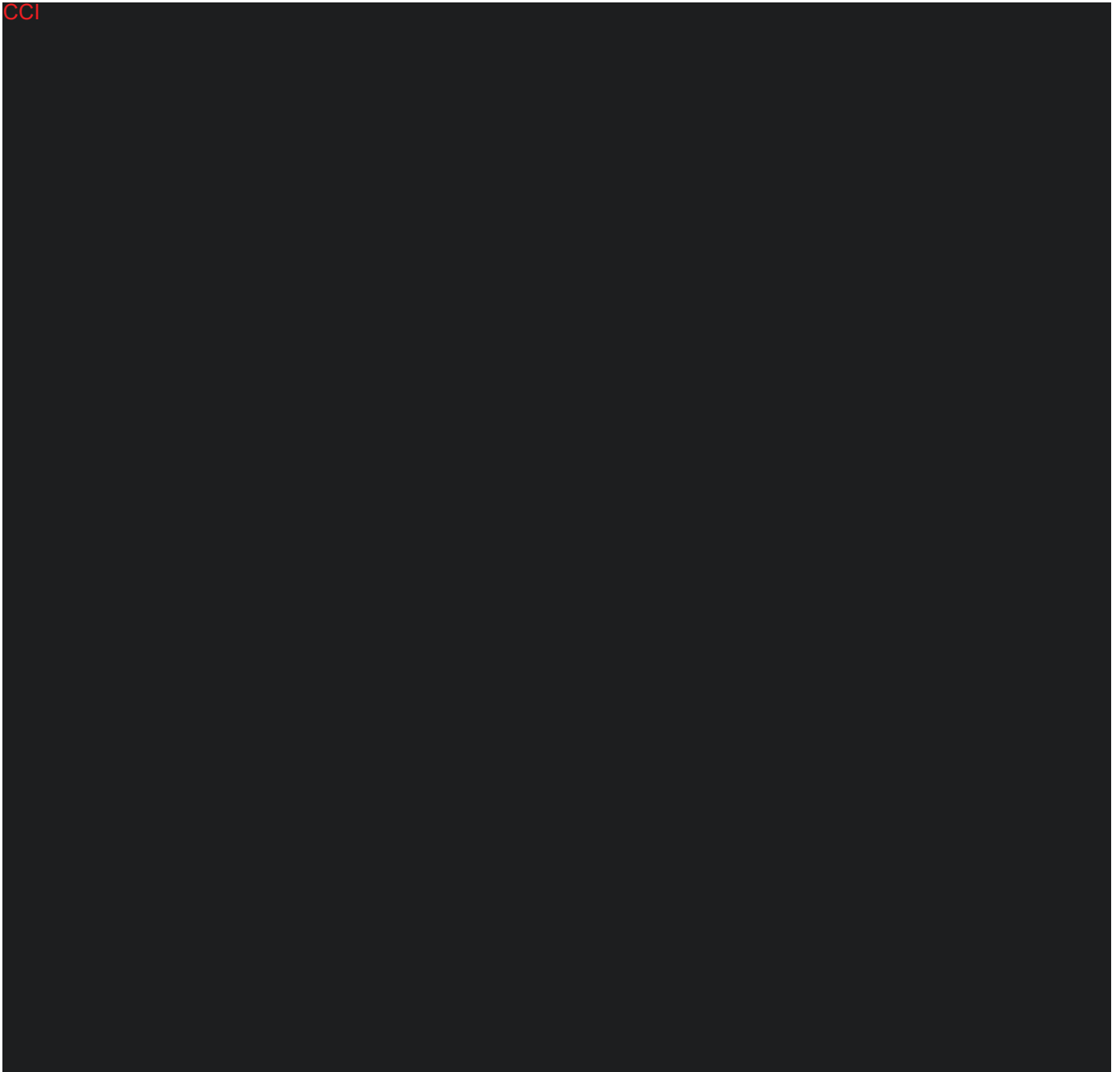
<b>Live Attenuated Vaccines</b>	
<b>Generic</b>	<b>Brand</b>
BCG (for tuberculosis)	Not available in the US
Herpes zoster vaccine	Zostavax
Influenza, intranasal	FluMist
Measles	Attenuvax
Measles, Mumps, and Rubella (MMR)	MMR
Mumps	Mumpsvox
Oral poliovirus vaccine, oral	OPV (no longer available in the 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

0909077671e08fa28815510p1tdvradflA approved on 24 Oct 2019 08:28 (GMT)



#### Appendix 4. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

CCI



Copyright©1996 Nicholas Bellamy  
All Rights Reserved

WOMAC NRS 3.1 – English for USA – V5

Page 1 of 6

CCI

WOMAC NRS 3.1 – English for USA – V5

PFIZER CONFIDENTIAL  
Page 131

## WOMAC Osteoarthritis Index NRS3.1

CCI



Copyright©1996 Nicholas Bellamy  
All Rights Reserved

WOMAC NRS 3.1 – English for USA – V5

Page 3 of 6

CCI

WOMAC NRS 3.1 – English for USA – V5

PFIZER CONFIDENTIAL  
Page 133

CCI

WOMAC NRS 3.1 – English for USA – V5

PFIZER CONFIDENTIAL  
Page 134

CCI

WOMAC NRS 3.1 – English for USA – V5

PFIZER CONFIDENTIAL  
Page 135



## **Appendix 5. Patient's Global Assessment of Osteoarthritis**

### **Patient's Global Assessment of Osteoarthritis – Knee**

Subjects will answer the following question when the knee is selected as index joint:

Considering all the ways your osteoarthritis in your knee affects you, how are you doing today?

Subjects will rate their condition using the following scale:

<b>Grade</b>	<b>Description</b>
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

### **Patient's Global Assessment of Osteoarthritis – Hip**

Subjects will answer the following question when the hip is selected as index joint:

Considering all the ways your osteoarthritis in your hip affects you, how are you doing today?

Subjects will rate their condition using the following scale:

<b>Grade</b>	<b>Description</b>
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

0909077671e08fa28845510prtdvafvaAprisovered00n.24.Fall-2019 08:28 (GMT)

## Appendix 6. Work Productivity and Activity Impairment Questionnaire: Osteoarthritis of the Knee or Hip V2.0 (WPAI:OA)

### Work Productivity and Activity Impairment Questionnaire: Osteoarthritis of the Knee or Hip V2.0 (WPAI:OA)

The following questions ask about the effect of your osteoarthritis of the knee or hip on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? \_\_\_\_\_ NO \_\_\_\_ YES  
*If NO, check "NO" and skip to question 6.*

The next questions are about the past seven days, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your osteoarthritis of the knee or hip? *Include hours you missed on sick days, times you went in late, left early, etc., because of your osteoarthritis of the knee or hip. Do not include time you missed to participate in this study.*

\_\_\_\_\_ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

\_\_\_\_\_ HOURS

4. During the past seven days, how many hours did you actually work?

\_\_\_\_\_ HOURS *(If "0", skip to question 6.)*

090907767e1e08fa28a155a0p1d1eaf1a4e9isovered00n.24 Feb 2019 08:28 (GMT)

- Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If osteoarthritis of the knee or hip affected your work only a little, choose a low number. Choose a high number if osteoarthritis of the knee or hip affected your work a great deal.*

Osteoarthritis of the knee or hip had no effect on my work

CIRCLE A NUMBER

- By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If osteoarthritis of the knee or hip affected your activities only a little, choose a low number. Choose a high number if osteoarthritis of the knee or hip affected your activities a great deal.*

Osteoarthritis of the knee or hip had no effect on my daily activities

CIRCLE A NUMBER

PFIZER CONFIDENTIAL  
Page 138

## Appendix 7. EuroQol 5 Dimension (EQ-5D-5L)

By placing a check mark in one box in each group below, please indicate which statements best describe your own health state today.

### Mobility

- I have no problems walking ☐
- I have slight problems walking ☐
- I have moderate problems walking ☐
- I have severe problems walking ☐
- I am unable to walk ☐

### Self-Care

- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ☐
- I have moderate problems washing or dressing myself ☐
- I have severe problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

### Usual Activities (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

### Pain/Discomfort

- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

### Anxiety/Depression

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

Continued to next page

0909077671@08Feb2018 15:53:00 n:\24-Feb-2018 08:28 (GMT)

We would like to know how good or bad your health is TODAY.

This scale is numbered from 0 to 100.

100 means the best health you can imagine.

0 means the worst health you can imagine.

Mark an X on the scale to indicate how your health is TODAY.

Now, please write the number you marked on the scale in the box below.

The best health  
you can imagine

100

95

90

85

80

75

70

65

60

55

50

45

40

35

30

25

20

15

10

5

0

Health State: \_\_\_\_\_

The worst health  
you can imagine

USA (English) © 2009 EuroQol Group. EQ-5D™ is a trade mark of the EuroQol Group

SAMPLE

0909077671e08f6a28c1550p100radf1A(apsisovered00)n.24-0ct-2019 08:28 (GMT)



[illegible]





9123

9123

5

1000000

SCORING, REFLEXES  
0 = NORMAL; 1 = DECREASED; 2 = ABSENT

0 = NORMAL; 1 = DECREASED; 2 = ABSENT

	RIGHT				LEFT			
Reflexes	N/A	0	1	2	N/A	0	1	2
25. Biceps brachii	○	○	○	○	○	○	○	○
26. Triceps brachii	○	○	○	○	○	○	○	○
27. Brachioradialis	○	○	○	○	○	○	○	○
28. Quadriceps femoris	○	○	○	○	○	○	○	○
29. Triceps surae	○	○	○	○	○	○	○	○

SCORING, SENSATION  
0 = NORMAL; 1 = DECREASED; 2 = ABSENT

SCORING, SENSATION

0 = NORMAL;    1 = DECREASED;    2 = ABSENT

0 = NORMAL; 1 = DECREASED; 2 = ABSENT

	RIGHT				LEFT			
<b>Sensation - I. Finger</b>	N/A	0	1	2	N/A	0	1	2
30. Touch pressure	○	○	○	○	○	○	○	○
31. Pin-prick	○	○	○	○	○	○	○	○
32. Vibration	○	○	○	○	○	○	○	○
33. Joint position	○	○	○	○	○	○	○	○
<b>Sensation - G. Toe</b>	N/A	0	1	2	N/A	0	1	2
34. Touch pressure	○	○	○	○	○	○	○	○
35. Pin-prick	○	○	○	○	○	○	○	○
36. Vibration	○	○	○	○	○	○	○	○
37. Joint position	○	○	○	○	○	○	○	○

9123



Administration of the PHQ-9 is not mandatory but may be used by the investigator to assess the severity of depression. The severity score is the sum of questions 1 through 9 only. A score of 15 or higher on questions 1 through 9 indicates severe depression. If used the PHQ-9 should be stored in the subject file. The results of this instrument will not be entered into a database, nor will it be analyzed.

Over the <u>last 2 weeks</u> , how often have you been bothered by the following problems?	Not at all (0)	Several days (1)	More than half the days (2)	Nearly every day (3)
1. Little interest or pleasure in doing things	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Feeling down, depressed, or hopeless	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Trouble falling or staying asleep, or sleeping too much	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Feeling tired or having little energy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Poor appetite or overeating	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Trouble concentrating on things, such as reading the newspaper or watching television	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Moving or speaking so slowly that other people could have noticed? Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Thoughts that you would be better off dead or of hurting yourself in some way	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?**

PHQ-9 is adapted from PRIME MD TODAY, developed by Drs Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues, with an educational grant from Pfizer Inc. For research information, contact Dr Kroenke at [kkroenke@regenstrief.org](mailto:kkroenke@regenstrief.org). Use of the PHQ-9 may only be made in accordance with the Terms of Use available of <http://www.pfizer.com>. Copyright ©1999 Pfizer Inc. All rights reserved. PRIME MD TODAY is a trademark of Pfizer Inc.

## Appendix 10. 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

0909077671e08fa28d15510p10vradf1A\approved00n.24.Fc01-2019 08:28 (GMT)

## Appendix 11. Survey of Autonomic Symptoms (SAS)<sup>55</sup>

**Table 1** Survey of Autonomic Symptoms<sup>a</sup>

Symptom/health problem	Q1a. Have you had any of the following health symptoms during the past 6 months? (1 = Yes; 0 = No)	Q1b. If you answered yes in Q1a, how much would you say the symptom bothers you? (1 = Not at all; 2 = A little; 3 = Some; 4 = A moderate amount; 5 = A lot)
1. Do you have lightheadedness?	1 0	1 2 3 4 5
2. Do you have a dry mouth or dry eyes?	1 0	1 2 3 4 5
3. Are your feet pale or blue?	1 0	1 2 3 4 5
4. Are your feet colder than the rest of your body?	1 0	1 2 3 4 5
5. Is sweating in your feet decreased compared to the rest of your body?	1 0	1 2 3 4 5
6. Is sweating in your feet decreased or absent (for example, after exercise or during hot weather)?	1 0	1 2 3 4 5
7. Is sweating in your hands increased compared to the rest of your body?	1 0	1 2 3 4 5
8. Do you have nausea, vomiting, or bloating after eating a small meal?	1 0	1 2 3 4 5
9. Do you have persistent diarrhea (more than 3 loose bowel movements per day)?	1 0	1 2 3 4 5
10. Do you have persistent constipation (less than 1 bowel movement every other day)?	1 0	1 2 3 4 5
11. Do you have leaking of urine?	1 0	1 2 3 4 5
12. Do you have difficulty obtaining an erection (men)?	1 0	1 2 3 4 5

\* Number of symptoms reported: \_\_\_\_\_ (sum of column A, 0-12 for men and 0-11 for women); total symptom impact score: \_\_\_\_\_ (sum of column B, 0-60 for men and 0-55 for women).

Example with 3 month recall period.

Health Care Resource Utilization

During the **last 3 months**, what services did you receive directly related to your osteoarthritis? (2/3)

	Number of Visits
<input type="checkbox"/> Orthopedist	<div>▲ ▲ ▲</div> <div>0 0 0</div> <div>▼ ▼ ▼</div>
<input type="checkbox"/> Physical Therapist	<div>▲ ▲ ▲</div> <div>0 0 0</div> <div>▼ ▼ ▼</div>
<input type="checkbox"/> Chiropractor	<div>▲ ▲ ▲</div> <div>0 0 0</div> <div>▼ ▼ ▼</div>
<input type="checkbox"/> Alternative Medicine or Therapy	<div>▲ ▲ ▲</div> <div>0 0 0</div> <div>▼ ▼ ▼</div>
<input type="checkbox"/> Podiatrist	<div>▲ ▲ ▲</div> <div>0 0 0</div> <div>▼ ▼ ▼</div>

2/3

Back Next




Health Care Resource Utilization

During the **last 3 months**, have you visited the emergency room due to your osteoarthritis?

☐ Yes ☐ No

How many times?

▲	▲	▲
0	0	0
▼	▼	▼

**Health Care Resource Utilization**

Did you use these aids or devices to help you in doing things because of your osteoarthritis in the **last 3 months**?

☐ Did not use any aids/ devices

☐ Walking aid

Never	Rarely	Sometimes	Often	Always
-------	--------	-----------	-------	--------

☐ Wheelchair

Never	Rarely	Sometimes	Often	Always
-------	--------	-----------	-------	--------

☐ Devices or utensils to help you dress, bathe or eat

Never	Rarely	Sometimes	Often	Always
-------	--------	-----------	-------	--------

☐ Other

Never	Rarely	Sometimes	Often	Always
-------	--------	-----------	-------	--------

Back 0% Next

Health Care Resource Utilization

**Thank you. You have completed this questionnaire.**

**If you would like to change any of your answers, you may do so by pressing the "Back" button prior to saving.**

**Please save your answers by pressing the "Save" button.**

**Once you press "Save", you will not be able to go back to review or change your answers.**

 Back



 Save



This is a list of abbreviations that may or may not be used in the protocol.

PFIZER CONFIDENTIAL  
Page 148

<b>Abbreviation</b>	<b>Term</b>
EDP	exposure during pregnancy
EDTA	edetic acid (ethylenediaminetetraacetic acid)
EQ-5D-5L	EuroQol 5 Dimension 5 Level
ER	extended release
ESR	erythrocyte sedimentation rate
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma glutamyltransferase
HBsAG	hepatitis B surface antigen
hCG	human Chorionic Gonadotropin
HCRU	Health Care Resource Utilization
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
hsCRP	high sensitivity C-reactive protein
ICH	International Conference on Harmonisation
ICRP	International Commission on Radiation Protection
ICTP	cross-linked carboxyterminal telopeptide of type I collagen
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
IL6	interleukin 6
IPAP	Initial Pain Assessment Period
IR	immediate release
IRT	interactive response technology
ITT	intent to treat
IUD	intrauterine device
IV	intravenous
IWRS	interactive web response system
KL	Kellgren-Lawrence
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

0909077571e08fa28815530p1010read1Aapproved00n.124-1011-2019 08:28 (GMT)

PFIZER CONFIDENTIAL  
Page 150

Abbreviation	Term
SNRI	serotonin norepinephrine reuptake inhibitor
SOA	schedule of activities
SOST	sclerostin
SPADI	Shoulder Pain and Disability Index
SPONK	spontaneous osteonecrosis of the knee
SRSD	single reference safety document
Tan	tanezumab
TNF- $\alpha$	tumor necrosis factor alpha
trkA	tropomyosin receptor kinase A
ULN	upper limit of normal
US	United States
VAS	visual analog scale
WHO	World Health Organization
WOMAC	Western Ontario and McMaster University Osteoarthritis Index
WPAI-OA	Work Productivity and Activity Impairment Questionnaire - Osteoarthritis

0909077671e08fa286155a0p1h0vradflA\aprisovered00n.124-0ct1-2019 08:28 (GMT)