CLINICAL PROTOCOL

A PHASE 3, RANDOMIZED, DOUBLE BLIND, PLACEBO AND ACTIVE-CONTROLLED, MULTICENTER, PARALLEL-GROUP STUDY OF THE ANALGESIC EFFICACY AND SAFETY OF TANEZUMAB IN ADULT SUBJECTS WITH CHRONIC LOW BACK PAIN

Compound:	PF-04383119
Compound Name:	Tanezumab
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trial Database (EudraCT) Number:	2012-005495-34
Protocol Number:	A4091059
Universal Trial Number:	U1111-1166-2271
Phase:	3

Document History

Document	Version Date	Summary of Changes
Amendment 3	18 July 2016	Inclusion criterion 5 was updated to allow prior inadequate treatment response to skeletal muscle relaxants to be considered as a protocol-qualifying medication. Exclusion criterion 2 was changed from BMI > 39 kg/m^2 to BMI ≥45 kg/m^2 Excusion criterion 7 was updated to remove the exclusion for closed worker's compensation claim, litigation, disasbility, or monetary settlement within 5 years. Administrative updates in Sections 5.8.1.4, 6.1.1, 7.3, 7.4.4, 9.2.2, Appendix 4 and Appendix 17 to: Clarify that facet joint injections and nerve blocks are prohibited beginning 30 days prior to IPAP and throughout Week 64. Clarify that all protocol-qualifying medications for chronic low back pain should be recorded on the eCRF. Incorporate changes outlined in a Protocol Administrative Change Letter which clarified the intended follow-up for subjects with severe and persistent joint pain. Clarify that the same step down testing strategy used for the primary endpoint will be employed for comparisons of tanezumab to tramadol treatment for the key secondary endpoint of change from Baseline to Week 16 for the average LBPI. Add eperisone to list of prohibited muscle relaxants in Appendix 4 and correct error in the spelling of "cyclobenzaprine." Add French country-specific administrative terms required for the Contrat Unique.

Amendment 2	26 August 2015	Change made in response to conditional approval of the clinical trials authorization (CTA) application for Spain, Hungary, Sweden, and Denmark using the Voluntary Harmonisation Procedure (VHP): For subjects participating in Europe, after the completion of the Week 16 visit and through to the Week 56 visit, the dose of tramadol PR or oral placebo may be decreased to a minimum of 100 mg per day, if clinically indicated. If the dose of tramadol PR or oral placebo is reduced, it may later be re-escalated for reasons of inadequate pain control to a maximum of the previous individually titrated dose. Wording describing this change was added to the Protocol Summary, Section 3.2, Section 5 (Table 3), Section 5.5.2, and Section 6.6. Wording below added to Section 6.6: Dose increases or decreases following the completion of the Week16 visit to the Week 56 will occur at scheduled or unscheduled clinic visits and will be accomplished by changing the dosage strength of the tablets that are dispensed to subjects. Wording below added to Section 9.2.2: Any additional sensitivity analyses of secondary efficacy endpoints to explore the potential difference between tramadol dosing post Week 16 in European subjects vs.subjects outside of Europe will be specified in the statistical analysis plan.
Amendment 1	27 July 2015	Change made in response to United States Food and Drug Administration Advice / Information Request (30 June 2015) for protocol A4091058: Required washout from rescue medication (acetaminophen / paracetamol) use before clinic visits has been decreased from 48 to 24 hours where applicable throughout the protocol.

		Clarification added that tramadol is not included in the opioid category as a protocol qualifying medication as defined in Section 4.1, Table 2. Clarification to the prohibited medications in Section 5.8.1 and Appendix 4, to specify that opioids analgesics are prohibited through Week 64. The Single Reference Safety Document cited in Protocol Section 1.2.8 has been updated and relevant text in Section 5.6 has been harmonized with this update. Definitions for completion of treatment and completion of study have been clarified in Protocol Section 3. Correction of minor inconsistencies in the protocol summary, Section 3 and Section 5.8.1.
Original protocol	1 April 2015	Not Applicable (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.

This is a list of abbreviations that may or may not be used in the protocol.	
Abbreviation	**Term**
ACR	American College of Rheumatology
ADA	anti-drug antibody
AE	adverse event
AEMPS	Agency on Medicinal Products and Medical Devices
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ASA	American Society of Anesthesiologists
AST	aspartate aminotransferase
BL	baseline
BMI	body mass index
BOCF	baseline observation carried forward
BP	blood pressure
BPI	Brief Pain Inventory
BUN	blood urea nitrogen
CCI [redacted]	[redacted]
CPK	creatine phosphokinase
CRF	case report form
CRA	Clinical Research Associate
CCI [redacted]	[redacted]
CSA	clinical study agreement
CTA	clinical trial application
CTS	carpal tunnel syndrome
CCI [redacted]	[redacted]
CYP	Cytochrome
DAAAP	US Food and Drug Administration's Division of Analgesia, Anesthetic, and Addiction Products
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
E-DMC	External Data Monitoring Committee
EDTA	edetic acid (ethylenediaminetetraacetic acid)
EQ-5D-5L	EuroQol 5 Dimension
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
Hb	Hemoglobin
CCI [redacted]	CCI [redacted]
HCRU	Health Care Resources Utilization
HIV	human immunodeficiency virus
HR	heart rate

[redacted]	[redacted]
ICH	International Conference on Harmonisation
ICRP	International Commission on Radiation Protection
[redacted]	[redacted]
ID	identification
IND	Investigational New Drug application
INR	International Normalized Ratio
IgG	immunoglobulin G
IgG2	immunoglobulin G Type 2
IRB	institutional review board
IL	interleukin
[redacted]	[redacted]
IPAP	Initial Pain Assessment Period
IRT	interactive response technology
ITT	intent to treat
IUD	intrauterine device
IV	intravenous
IWRS	interactive web response system
LBPI	Low Back Pain Intensity
LDH	lactate dehydrogenase
LFT	liver function test
LOCF	Last Observation Carried Forward
LSLV	last subject last visit
LSMean	least squared mean
MAO	Monoamine oxidase inhibitors
MDA	Multi-Domain Average
MHRA	United Kingdom's Medicines and Healthcare products Regulatory Agency
[redacted]	[redacted]
mPRTI	Patient Reported Treatment Impact Assessment-Modified
MRI	magnetic resonance imaging
mSv	millisievert
N/A	not applicable
NGF	nerve growth factor
NGFI	nerve growth factor inhibitor
NIH	National Institutes of Health
NIS	Neuropathy Impairment Score
NRS	numeric rating scale
NSAID	non-steroidal anti-inflammatory drug
NSC	Neuropathy Symptom Change Questionnaire
NYHA	New York Heart Association
OA	osteoarthritis
[redacted]	[redacted]
OTC	over-the-counter
PCD	primary completion date
PD	pharmacodynamic
PEI	Paul Ehrlich Institute
PHQ-9	Patient Health Questionnaire-9

PFS	pre-filled syringe
PGA	Patient Global Assessment
[redacted]	[redacted]
PK	pharmacokinetic
PR	Prolonged Release
PT	prothrombin time
PTT	partial thromboplastin time
QT	in electrocardiography, the time corresponding to the beginning of depolarization to repolarization of the ventricles
QTc	in electrocardiography, the time corresponding to the beginning of depolarization to repolarization of the ventricles, corrected for heart rate
QTcB	QT corrected for heart rate using Bazett's formula
QTcF	QT corrected for heart rate using Fridericia's formula
RA	Rheumatoid Arthritis
RMDQ	Roland Morris Disability Questionnaire
RNA	ribonucleic acid
RPOA	rapidly-progressive osteoarthritis
SAE	serious adverse event
SAPS	Self-Administered Patient Satisfaction Scale
SAS	Survey of Autonomic Symptoms
SC	subcutaneous
SNRI	serotonin norepinephrine reuptake inhibitor
SOA	schedule of activities
[redacted]	[redacted]
SPADI	Shoulder Pain and Disability Index
SPONK	spontaneous osteonecrosis of the knee
SRSD	single reference safety document
TENS	transdermal electroneural stimulation
TNF-α	tumor necrosis factor alpha
trkA	tropomyosin receptor kinase A
TSQM	Treatment Satisfaction Questionnaire for Medication
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:LBP	Work Productivity and Activity Impairment Questionnaire: Low Back Pain

PROTOCOL SUMMARY

Background

Tanezumab is a monoclonal antibody that binds to and inhibits the actions of nerve growth factor (NGF). The Nerve Growth Factor Inhibitor (NGFI) class may offer an important breakthrough in the treatment of chronic pain and is under clinical investigation for the treatment of pain associated with osteoarthritis or other chronic pain conditions.

The completed Phase 2 and Phase 3 studies conducted to date have demonstrated that tanezumab is efficacious and generally safe and well tolerated for the treatment of pain due to osteoarthritis and chronic low back pain. In addition, completed Phase 1/2 studies suggest tanezumab is also efficacious and generally safe for the treatment of neuropathic, visceral, and cancer pain.

In 2010, the United States (US) Food and Drug Administration's (FDA) Division of Analgesia, Anesthetic, and Addiction Products (DAAAP) placed tanezumab (June/July 2010) and subsequently the entire Nerve Growth Factor Inhibitor (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.[1] On March 12, 2012, the FDA Arthritis Advisory Committee reviewed these results as well as those prepared by the FDA.[2,3] 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 chronic low back pain, 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 and are incorporated in the design and objectives of this 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 function study in non-human primates, functional changes in the cardiovascular system controlled by the sympathetic nervous system were not observed.

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.

This study will investigate the efficacy and safety of a fixed dose of tanezumab 5 mg and 10 mg administered subcutaneously (SC) seven times at 8-week intervals. The primary objective of this study is to demonstrate superior efficacy of tanezumab 10 mg and 5 mg administered SC every 8 weeks compared to placebo at Week 16. The study will provide additional experience with the tanezumab 5 mg and 10 mg doses which have been shown to provide efficacy benefits with a favorable safety profile in a previous Phase 2 clinical trial. In addition, the study will evaluate the long term safety profile of tanezumab treatment for chronic low back pain compared to tramadol Prolonged Release (PR), a medication commonly utilized for the treatment of chronic low back pain.

In order to optimize the potential benefit-risk relationship, the study will be conducted in subjects with moderate to severe chronic low back pain without comorbid symptomatic osteoarthritis who have had inadequate pain relief or are unable to take most conventional pharmacological treatment options for low back pain.

STUDY OBJECTIVES AND ENDPOINTS

Primary Objective:

- Demonstrate superior analgesic efficacy of tanezumab 10 mg and 5 mg administered subcutaneously (SC) every 8 weeks compared to placebo at Week 16.

Secondary Objectives:

- Evaluate the long-term safety of tanezumab 10 mg and 5 mg SC administered every 8 weeks (7 administrations);

- Estimate the long-term analgesic efficacy of tanezumab 10 mg and 5 mg SC administered every 8 weeks (7 administrations) up to Week 56;

- Compare the analgesic efficacy of tanezumab 10 mg SC administered every 8 weeks relative to an active comparator (oral tramadol PR) at Week 16.

Primary Endpoint:

- Change from Baseline to Week 16 in the daily average Low Back Pain Intensity (LBPI) score as measured by an 11-point Numeric Rating Scale for tanezumab vs placebo.

Key Secondary Endpoints:

- Change from Baseline to Week 16 in the Roland Morris Disability Questionnaire (RMDQ) for tanezumab vs placebo;

- Change from Baseline to Week 16 in the daily average LBPI score as measured by an 11-point Numeric Rating Scale for tanezumab vs tramadol.

Additional Secondary Endpoints

Efficacy Measures:

- Change from Baseline to Weeks 2, 4, 8, 12, 24, 32, 40, 48, 56, and 64 in average LBPI score;

- Change from Baseline to Weeks 2, 4, 8, 16 (for tanezumab vs tramadol), 24, 32, 40, 48, 56, 64, and 80 in RMDQ total score;

- Change from Baseline to Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, and 64 in Patient's Global Assessment of Low Back Pain;

- Cumulative distribution of percent change from Baseline in average LBPI score to Weeks 16, 24, and 56 (endpoint for summary only);

- Response as defined by a ≥30%, ≥50%, ≥70% and a ≥90% reduction from Baseline in daily average LBPI score derived from the subject diary at Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, 56, and 64;

- Response as defined by a ≥30%, ≥50%, ≥70% and a ≥90% reduction from Baseline in the RMDQ score at Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, 64 and 80;

- Cumulative distribution of percent change from Baseline in RMDQ score to Weeks 16, 24, and 56 (endpoint for summary only);

- Change from Baseline to Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, and 64 in the Brief Pain Inventory-short form (BPI-sf) scores for Worst Pain, Average Pain, Pain Interference Index (composite function score), Pain Interference with General Activity, Pain Interference with Walking Ability, Pain Interference with Sleep, and Pain Interference with Normal Work;

- Chronic Low Back Pain Responder Index analysis [composite endpoint of average LBPI score, Patient's Global Assessment of Low Back Pain, and RMDQ total score] at Weeks 2, 4, 8, 16, 24, 32, 40, 48 and 56;

- Treatment Response: Improvement of ≥2 points in Patient's Global Assessment of Low Back Pain at Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, and 64;

- Euro Quality of Life Health State Profile (EQ-5D-5L™) dimensions and overall health utility score at Baseline, Weeks 8, 16, 24, 40, 56, and 64;
- Work Productivity and Activity Impairment Questionnaire: Low Back Pain (WPAI:LBP) change from Baseline to Weeks 16, 56, and 64 in the percent work time missed due to chronic low back pain, percent impairment while working due to chronic low back pain, percent overall work impairment due to chronic low back pain, and percent activity impairment due to chronic low back pain;
- Incidence of and time to discontinuation due to lack of efficacy;
- Usage of rescue medication (incidence, and number of days of usage) during Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, 56 and Week 64.
- Usage of rescue medication (amount taken) during Weeks 2, 4, 8, 12 and 16;
- Health Care Resource Utilization at Baseline, Weeks 64, and 80.

Treatment Satisfaction Measures:

- Treatment Satisfaction Questionnaire for Medication v.II (TSQM) score at Weeks 16 and 56;
- Patient Reported Treatment Impact Assessment-Modified (mPRTI) at Weeks 16 and 56.

Safety Measures:

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

- Physical examinations.

Tertiary Endpoints

- Plasma tanezumab concentrations;
- Serum NGF assessments;
- Serum and urine osteoarthritis biomarker concentrations;
- NIH (National Institutes of Health) Pain Consortium Chronic Low Back Pain (CLBP) Minimum Dataset at Baseline, Weeks 16 and 56.

STUDY DESIGN

This is a randomized, double-blind, placebo- and active-controlled, multicenter, parallel-group Phase 3 study of the efficacy and safety of tanezumab when administered by SC injection for up to 56 weeks in adult subjects with chronic low back pain. Approximately 1800 subjects will be randomized to 1 of 4 treatment groups in a 2:2:2:3 ratio (ie, 400 subjects per treatment group for the placebo, tanezumab 5 mg and tanezumab 10 mg treatment groups and 600 subjects in the tramadol PR treatment group). Treatment groups will include:

1. Placebo administered SC at an 8-week interval plus placebo matching tramadol PR up to Week 16. At the Week 16 visit, subjects in this group will be switched in a blinded fashion in a 1:1 ratio to either tanezumab 5 mg or tanezumab 10 mg administered SC at an 8 week interval plus placebo matching tramadol PR to Week 56;
2. Tanezumab 5 mg SC administered at an 8-week interval plus placebo matching tramadol PR to Week 56;
3. Tanezumab 10 mg SC administered at an 8-week interval plus placebo matching tramadol PR to Week 56;
4. Oral tramadol PR plus placebo administered SC at an 8-week interval to Week 56.

The study is designed with a total duration (post randomization) of up to 80 weeks and will consist of three periods: Screening (up to 37 days; includes a Washout Period and an Initial Pain Assessment Period), a Double-blind Treatment Period (comprised of a 16-week Primary Efficacy Phase and a 40-week Long Term Safety and Efficacy Phase), and a Follow-up Period (24 weeks).

Prior to entering the study, subjects must have a documented history of previous inadequate treatment response to medications in 3 different categories of agents commonly used to treat and generally considered effective for the treatment of chronic low back pain. During the Screening Period, all subjects will undergo X-rays of the hips, knees and shoulders as well as X-rays of other joints with signs and symptoms of osteoarthritis. The X-rays will be assessed by a central radiology reader to determine subject radiographic eligibility for study participation.

Administration of SC study medication (placebo, tanezumab 5 mg or tanezumab 10 mg) will occur at Baseline, Weeks 8, 16, 24, 32, 40 and 48. Oral tramadol PR or matching placebo will be self administered by subjects on a daily basis from Baseline through Week 56. During Weeks 1 through 4 subjects may titrate the dose of oral medication upward or downward depending on pain relief and tolerability. The maximum dose of tramadol PR will be 300 mg per day. From the Week 4 visit through to Week 56 the dose of oral study medication must remain stable. *Note: For subjects participating in Europe, following the completion of the Week 16 visit through the Week 56 visit, the dose of tramadol PR or oral placebo may be decreased to a minimum of 100 mg per day, if clinically indicated. If the dose of tramadol PR or oral placebo is reduced, it may later be re-escalated for reasons of inadequate pain control to a maximum of the previous individually titrated dose (See Section 5.5.2).* At the Week 16 visit, the reduction in LBPI score from Baseline will be calculated and only subjects meeting pre-defined response criteria may continue in the study. Also at the Week 16 visit, subjects in the placebo treatment arm will be switched in a blinded manner to tanezumab SC treatment, provided they meet the efficacy response criteria to continue in the study. These subjects will be switched in a 1:1 ratio to tanezumab 5 mg or tanezumab 10 mg SC plus matching placebo and will receive the first administration of SC tanezumab at Week 16. At Week 32, subjects must again meet the efficacy responder criteria to continue study treatment. The Long Term Safety and Efficacy Phase begins after the Week 16 visit and continues until Week 56. At Week 56, subjects will enter the Follow-up Period which lasts until Week 80.

Subjects who discontinue from treatment prior to Week 56 will be required to undergo 24 weeks of follow-up.

X rays of the hips, knees and shoulders as well as any additional joint that was imaged at Screening will be obtained for all subjects at Weeks 24, 56 and 80. These images will be sent to the Central Reader for review. At Week 24, confirmation of the continuing radiographic eligibility of the subject must be received from the Central Reader prior to administration of the Week 24 SC study medication.

Subjects who have undergone or plan to undergo total joint replacement or other arthroplasty procedure during the study will be discontinued from study treatment. 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 substudy or a separate protocol, provided the subject consents.

STATISTICAL METHOD

A minimum sample size of approximately 400 subjects per treatment group are needed to provide at least 80% power to achieve statistical significance (at the 5% two-sided level) for both comparisons of tanezumab 10 mg and 5 mg versus placebo as well as the comparison of tanezumab 10 mg versus active comparator in the primary endpoint, Change from Baseline to Week 16 in the average LBPI score. Since placebo subjects reaching Week 16 response criteria will be switched to tanezumab treatment only, in order to balance subject exposure during the safety phase of the trial (post Week 16) the number of subjects randomized at Baseline to the active comparator group is increased to 600. The total sample size will be approximately 1800 subjects.

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

The primary efficacy endpoint will be analyzed using an analysis of covariance (ANCOVA) model, with model terms for Baseline score 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. First, the tanezumab 10 mg treatment group will be tested versus placebo, and if statistically significant ($p \leq 0.05$) then the tanezumab 5 mg treatment group will be tested versus placebo. This testing procedure will maintain the Type I error to 5% or less. The same step-down testing strategy used for the primary endpoint will be employed for comparisons of tanezumab to tramadol treatment for the key secondary endpoint of change from Baseline to Week 16 for the average LBPI. These comparisons will be made conditional on the primary efficacy comparisons. For the key secondary objective of tanezumab versus placebo for change from Baseline to Week 16 for the RMDQ, these treatment comparisons will be made conditional on the primary efficacy comparisons. In particular, tanezumab 10 mg versus placebo for RMDQ will be tested if tanezumab 10 mg versus placebo for average LBPI is significant ($p \leq 0.05$), and then tanezumab 5 mg versus placebo for RMDQ will be tested if both (1) tanezumab 10 mg versus placebo for RMDQ and (2) tanezumab 5 mg versus placebo for average LBPI are significant ($p \leq 0.05$). Use of the step-down testing will ensure the type I error is maintained to 5% or less within each of the key secondary objectives.

The key secondary endpoint of RMDQ will be analyzed using an ANCOVA model, with model terms for Baseline score, Baseline LBPI score, treatment group, and study site as a random effect.

The primary analysis of the primary endpoint and the key secondary endpoints will use multiple imputations 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.

Standard safety reporting tables will summarize and list the safety data.

DATA MONITORING COMMITTEE

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

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures and Assessments sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

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

Schedule of Activities: Baseline through Week 56

	Screen		Treatment Phase										
Visit Indentifiers		**IPAP**	**Baseline[b]**	**Weeks 1, 3**	**Week 2**	**Week 4**	**Week 8**	**Week 12[d]**	**Week 16 Primary Efficacy timepoint**	**Week 24**	**Weeks 32, 40, 48**	**Weeks 20, 28, 36, 44, 52[d]**	**Week 56/End of Treatment**
Study Activities[a]	**Day -37 to -6**	**Day-5 to -1**	**Day 1 Dosing Visit**	**(±2 days) Telephone Contact[c]**	**Day 15 (±2 days)**	**Day 29 (±3 days)**	**Day 57 (±7 days) Dosing Visit**	**(±7 days) Telephone Contact**	**Day 113 (±7 days) Dosing Visit**	**(±7 days) Dosing Visit**	**(±7 days) Dosing Visits**	**(±7 days) Telephone Contact**	**Day 393 (±7 days)**
Informed Consent	X												
Inclusion/Exclusion Criteria/ subject eligibility	X		X										
Demographics, General and Musculoskeletal Specific Medical History and Prior/Current Medication Use	X												
Primary Diagnosis/	X												
Quebec Task Force Category	X												

	Screen		Treatment Phase										
Visit Indentifiers		**IPAP**	**Baseline**[b]	**Weeks 1, 3**	**Week 2**	**Week 4**	**Week 8**	**Week 12**[d]	**Week 16 Primary Efficacy timepoint**	**Week 24**	**Weeks 32, 40, 48**	**Weeks 20, 28, 36, 44, 52**[d]	**Week 56/End of Treatment**
Study Activities[a]	**Day -37 to -6**	**Day-5 to -1**	**Day 1 Dosing Visit**	**(±2 days) Telephone Contact**[c]	**Day 15 (±2 days)**	**Day 29 (±3 days)**	**Day 57 (±7 days) Dosing Visit**	**(±7 days) Telephone Contact**	**Day 113 (±7 days) Dosing Visit**	**(±7 days) Dosing Visit**	**(±7 days) Dosing Visits**	**(±7 days) Telephone Contact**	**Day 393 (±7 days)**
Height/BMI/ Smoking Status/Female Hormonal Status/Alcohol Use	X												
Body Weight	X												X
Health Care Resource Utilization (HCRU)			X										
Vital Signs (sitting BP, HR)	X		X		X	X	X		X	X	X		X
Orthostatic Blood Pressure (supine/standing)	X		X		X	X	X		X	X	X		X
Electrocardiogram (12-lead)	X								X				X
General Physical Examination	X												X
Musculoskeletal Physical Examination	X		X		X	X	X		X	X	X		X
Neurologic Exam/Neuropathy Impairment Score (NIS)[e]	X		X		X	X	X		X	X	X		X
Adverse event assessment			X	X	X	X	X	X	X	X	X	X	X

	Screen		Treatment Phase										
Visit Indentifiers		**IPAP**	**Baseline**[b]	**Weeks 1, 3**	**Week 2**	**Week 4**	**Week 8**	**Week 12**[d]	**Week 16 Primary Efficacy timepoint**	**Week 24**	**Weeks 32, 40, 48**	**Weeks 20, 28, 36, 44, 52**[d]	**Week 56/End of Treatment**
Study Activities[a]	**Day -37 to -6**	**Day-5 to -1**	**Day 1 Dosing Visit**	**(±2 days) Telephone Contact**[c]	**Day 15 (±2 days)**	**Day 29 (±3 days)**	**Day 57 (±7 days) Dosing Visit**	**(±7 days) Telephone Contact**	**Day 113 (±7 days) Dosing Visit**	**(±7 days) Dosing Visit**	**(±7 days) Dosing Visits**	**(±7 days) Telephone Contact**	**Day 393 (±7 days)**
Review weekly joint pain scores			X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review			X	X	X	X	X	X	X	X	X	X	X
Patient Reported Assessments Completed at Study Visits (collected via tablet device at site)													
BPI-sf			X		X	X	X		X	X	X		X
RMDQ			X		X	X	X		X	X	X		X
Patient Global Assessment of Low Back Pain			X		X	X	X		X	X	X		X
Pain DETECT			X										
WPAI:LBP			X						X				X
EQ-5D-5L			X				X		X	X	X[f]		X
NIH CLBP Min Dataset			X						X				X
TSQM									X				X
mPRTI									X				X
Survey of Autonomic Symptoms (SAS)	X									X			X
Subject Daily and Weekly Assessments (via IRT)													
LBPI score and rescue medication usage[g]	X[h]	---------- (Daily via IRT [handheld device])----------								---------- (Weekly via IRT [handheld device])------			
Record joint pain in major joints, if applicable[i]	X	---------- (Weekly via IRT [handheld device])----------											

	Screen		Treatment Phase										
Visit Indentifiers		**IPAP**	**Baseline**[b]	**Weeks 1, 3**	**Week 2**	**Week 4**	**Week 8**	**Week 12**[d]	**Week 16 Primary Efficacy timepoint**	**Week 24**	**Weeks 32, 40, 48**	**Weeks 20, 28, 36, 44, 52**[d]	**Week 56/End of Treatment**
Study Activities[a]	**Day -37 to -6**	**Day-5 to -1**	**Day 1 Dosing Visit**	**(±2 days) Telephone Contact**[c]	**Day 15 (±2 days)**	**Day 29 (±3 days)**	**Day 57 (±7 days) Dosing Visit**	**(±7 days) Telephone Contact**	**Day 113 (±7 days) Dosing Visit**	**(±7 days) Dosing Visit**	**(±7 days) Dosing Visits**	**(±7 days) Telephone Contact**	**Day 393 (±7 days)**
Concomitant NSAID usage			---------- (Weekly via IRT [handheld device])----------										
Radiographic Assessments													
X-rays of the hips, knees and shoulders	X									X[j]			X
Central reader to confirm radiologic eligibility	X									X[j]			
Compliance assessments													
Assess compliance with oral study medication				X	X	X	X	X	X	X	X	X	X
Compliance with daily and weekly diary entries via IRT			X	X	X	X	X	X	X	X	X	X	X
Rescue medication compliance			X	X	X	X	X	X	X	X	X	X	X
NSAID limit compliance				X	X	X	X	X	X	X	X	X	X
Remind subject of contraceptive requirements	X		X	X	X	X	X	X	X	X	X	X	X
Laboratory													
Hepatitis Screen (Hepatitis B & C); HIV, Urine Toxicology screen	X												

	Screen		Treatment Phase										
Visit Indentifiers		**IPAP**	**Baseline**[b]	**Weeks 1, 3**	**Week 2**	**Week 4**	**Week 8**	**Week 12**[d]	**Week 16 Primary Efficacy timepoint**	**Week 24**	**Weeks 32, 40, 48**	**Weeks 20, 28, 36, 44, 52**[d]	**Week 56/End of Treatment**
Study Activities [a]	**Day -37 to -6**	**Day-5 to -1**	**Day 1 Dosing Visit**	**(±2 days) Telephone Contact**[c]	**Day 15 (±2 days)**	**Day 29 (±3 days)**	**Day 57 (±7 days) Dosing Visit**	**(±7 days) Telephone Contact**	**Day 113 (±7 days) Dosing Visit**	**(±7 days) Dosing Visit**	**(±7 days) Dosing Visits**	**(±7 days) Telephone Contact**	**Day 393 (±7 days)**
Hemoglobin A1c	X												
Serum FSH testing[k]	X												
Serum/Urine Pregnancy Test[l]	X		X				X		X	X	X		X
Hematology	X		X						X				
Blood Chemistry	X		X						X				
Urinalysis	X												
Serum/Plasma Retention Sample			X						X				X
Plasma Pharmacokinetic sample[m]			X		X[m]	X[m]	X		X		X[n]		X
Serum Pharmacodynamic sample (NGF)[m]			X		X	X	X				X[n]		X
Serum Anti-Drug Antibody[m]			X				X		X		X[n]		X
Serum and urine biomarkers [o]			X										
Banked biospecimen (whole blood)			X										
Trial Treatment													
Assess treatment response and eligibility to continue in the trial[p]									X[p]		X[p]		
Randomization			X										

	Screen		Treatment Phase										
Visit Indentifiers		**IPAP**	**Baseline**[b]	**Weeks 1, 3**	**Week 2**	**Week 4**	**Week 8**	**Week 12**[d]	**Week 16 Primary Efficacy timepoint**	**Week 24**	**Weeks 32, 40, 48**	**Weeks 20, 28, 36, 44, 52**[d]	**Week 56/End of Treatment**
Study Activities[a]	**Day -37 to -6**	**Day-5 to -1**	**Day 1 Dosing Visit**	**(±2 days) Telephone Contact**[c]	**Day 15 (±2 days)**	**Day 29 (±3 days)**	**Day 57 (±7 days) Dosing Visit**	**(±7 days) Telephone Contact**	**Day 113 (±7 days) Dosing Visit**	**(±7 days) Dosing Visit**	**(±7 days) Dosing Visits**	**(±7 days) Telephone Contact**	**Day 393 (±7 days)**
SC Study medication			X				X		X	X	X		
Blinded Oral Study Medication			----------X----------										
Adjust oral study medication based on pain relief and tolerability[q]				X	X	X			(X[r])	(X[r])	(X[r])		
Dispense Blinded Oral Study Medication			X		X	X	X		X	X	X		
Dispense rescue medication	X		X		X	X	X		X	X	X		X

Schedule of Activities: Follow-Up Period

Study Activities	Follow-Up Period				Early Termination (ET) Procedures				
	Week 60	**Week 64**	**Week 68, 72, 76**	**Week 80 End of Study**	**ET Visit 1**	**ET Telephone Contact**	**ET Visit 2**	**ET Telephone Contact**	**Final ET Visit**
	(±7 days) Tele phone Contact	**Day 449 (±7 days)**	**(±7 days) Tele phone Contact**	**Day 560 (±7 days)**	**8 weeks after last dose of SC Study Med (±7 days)**	**12 weeks after last dose of SC Study Med (±7 days)**	**16 Weeks after last dose of SC Study Med (±7 days)**	**20 weeks after last dose of SC Study Med (±7 days)**	**24 Weeks after last dose of SC Study Med (±7 days)**
Vital Signs (sitting BP, HR)		X		X	X		X		X
Orthostatic Blood Pressure (supine/standing)		X		X	X		X		X
12-lead ECG				X	X				X
Body weight					X				
General Physical Examination					X				
Musculoskeletal Physical Examination		X		X	X		X		X
Neurologic Exam/Neuropathy Impairment Score (NIS)[e]		X		X	X		X		X
Adverse event assessment	X	X	X	X	X	X	X	X	X
Review weekly joint pain scores	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X
Patient Reported Assessments Completed at Study Visits (collected via tablet device at site)									
BPI-sf		X			X		X		
RMDQ		X		X	X		X		X
Patient Global Assessment of Low Back Pain		X			X		X		
WPAI:LBP		X			X		X		
EQ-5D-5L		X			X		X		
NIH CLBP Min Dataset					X				
HCRU		X		X			X		X
TSQM					X				
mPRTI					X				

Study Activities	Follow-Up Period				Early Termination (ET) Procedures				
	Week 60	Week 64	Week 68, 72, 76	Week 80 End of Study	ET Visit 1	ET Telephone Contact	ET Visit 2	ET Telephone Contact	Final ET Visit
	(±7 days) Tele phone Contact	Day 449 (±7 days)	(±7 days) Tele phone Contact	Day 560 (±7 days)	8 weeks after last dose of SC Study Med (±7 days)	12 weeks after last dose of SC Study Med (±7 days)	16 Weeks after last dose of SC Study Med (±7 days)	20 weeks after last dose of SC Study Med (±7 days)	24 Weeks after last dose of SC Study Med (±7 days)
Survey of Autonomic Symptoms questionnaire				X	X				X
Subject Weekly Assessments (IRT)									
LBPI score[g]	----------X------				----------X----------				
Rescue medication use[g]	----------X----------				----------X----------				
Record joint pain, if applicable[i]	----------X----------				----------X----------				
Concomitant NSAID usage	----------X----------				----------X----------				
Radiographic Assessments									
X rays of the hips, knees and shoulders				X	X				X
Compliance assessments									
Compliance with daily and weekly diary entries via IRT	X	X	X		X	X	X	X	
Rescue medication compliance	X	X			X	X	X		
NSAID limit compliance	X	X			X	X	X		
Remind subject of contraceptive requirement	X	X			X	X	X		
Laboratory									
Serum/Urine Pregnancy Test[l]		X			X		X		
Hematology		X					X		
Blood Chemistry		X					X		
Serum/Plasma Retention Sample		X			X		X		
Plasma Pharmacokinetic sample		X			X		X		
Serum Pharmacodynamic sample (NGF)		X			X		X		

Study Activities	Follow-Up Period				Early Termination (ET) Procedures				
	Week 60	Week 64	Week 68, 72, 76	Week 80 End of Study	ET Visit 1	ET Telephone Contact	ET Visit 2	ET Telephone Contact	Final ET Visit
	(±7 days) Tele phone Contact	Day 449 (±7 days)	(±7 days) Tele phone Contact	Day 560 (±7 days)	8 weeks after last dose of SC Study Med (±7 days)	12 weeks after last dose of SC Study Med (±7 days)	16 Weeks after last dose of SC Study Med (±7 days)	20 weeks after last dose of SC Study Med (±7 days)	24 Weeks after last dose of SC Study Med (±7 days)
Serum Anti-Drug Antibody		X		X	X		X		X
Trial Treatment									
Dispense rescue medication		X			X		X		
Assign standard of care treatment as needed		X					X		

a. Refer to Section 6 for the order in which study procedures are to be conducted.

b. All study activities at Baseline (Day 1) should be performed prior to dosing with study medication, unless otherwise noted.

c. Telephone contact with the subject should be made at Weeks 1 and 3 to counsel the subject regarding adjustment of the oral study medication.

d. Telephone Contact Visit: If adverse events dictate that the subject should be seen, an unscheduled visit may be conducted and pertinent exams conducted (eg, physical exam, neurological exam, ECG, clinical laboratory testing) depending on the nature of the event and the Investigator's clinical judgment.

e. A neurological examination (NIS) will be performed by the Investigator (or designated physician) and assessed for clinically significant changes from Baseline.

f. EQ-5D-5L to be conducted at Week 40 only.

g. LBPI scores and rescue medication use are collected daily using IRT up to Week 16. After Week 16 LBPI scores and rescue medication will be collected weekly via IRT. LBPI scores are collected until Week 64, rescue medication usage is collected to Week 80.

h. At the Screening visit only, in order to determine eligibility, the LBPI score will be collected via the IRT.

i. Collected at Screening and then weekly thereafter as described Section 7.3.2.

j. At Week 24, sites must receive confirmation of continued radiologic eligibility from the Central Reader prior to administering the Week 24 SC study medication. Refer to Section 6.11.1.

k. FSH testing in female subjects as described in Section 7.3.4.4.

l. Serum pregnancy tests are obtained at Screening, Weeks 56 and 64 or Early Termination Visits 1 and 2 for subjects who discontinue (Refer to Section 6.20). A urine pregnancy test will be obtained at Baseline prior to initial dosing, and pre-dose at Weeks 8, 16, 24, 32, 40, and 48.

m. On dosing visits, samples for ADA, PK, and NGF should be obtained pre-dose. At Weeks 2 and 4 PK and NGF will be at measured at selected sites only.

n. Of the 3 dosing visits listed, obtain a sample for ADA, PK, at Weeks 32 and 48 and for PD (NGF) at Week 48 only.

o. Biomarker samples should be collected prior to dosing and, if possible, following a fasting period of at least 8 hours at approximately the same time of day at all scheduled timepoints. Urine collected for biomarkers should be the second or later void of the day.

p. At the Week 16 visit, all subjects must have at least a 30% reduction in average LBPI score relative to Baseline and at least a 15% reduction in mean weekly LBPI score from Baseline at any week from Week 1 to Week 15 in order to continue study treatment. In addition, at the Week 32 visit, all subjects must have at least a 30% reduction in average LBPI score relative to Baseline in order to continue study treatment. Subjects who do not meet these response criteria will be discontinued from the Treatment Period and enter Early Termination Follow-up Period (See Section 6.20.1).

q. Refer to Section 6.5.

r. For subjects participating in Europe, following the completion of the Week 16 visit through the Week 56 visit, the dose of tramadol PR or oral placebo may be decreased to a minimum of 100 mg per day, if clinically indicated. If the dose of tramadol PR or oral placebo is reduced, it may later be re-escalated to a maximum of the previous individually titrated dose (See Section 5.5.2).

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1. INTRODUCTION

1.1. Mechanism of Action/Indication

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

1.2. Background and Rationale

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

During mammalian development, nerve growth factor (NGF) is required for the survival and growth of several populations of neurons. In adults, the effect of NGF signaling shifts from the regulation of neuronal survival to the regulation of neuronal phenotype and function. The role of NGF in the adult mammal appears to principally be as a modulator of nociceptive neuronal activity. Thus, NGF plays an important role in modulation of the pain response.[4,5] Many studies employing a variety of antibodies to NGF or tropomyosin receptor kinase A (trkA)-IgG fusion protein have demonstrated that blocking NGF bioactivity normalizes pain sensitivity, particularly in states of allodynia and hypersensitivity, following a variety of insults such as Freund's adjuvant, carrageenan, or surgical incision.[5,6]

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

Dysregulation of NGF has been specifically implicated in pain in the lumbar spine. In clinical studies, there is increased nerve density accompanied by increased NGF in painful discs as compared to discs removed from non-painful levels.[9,10] In addition, rodent studies have shown that the vast majority of fibers innervating discs express NGF receptors.[11] The injection of exogenous NGF into the multifidus muscle of the lower back in rats sensitizes the response of neurons projecting to this muscle to mechanical stimulation.[12]

1.2.2. Description of Investigational Product

Tanezumab is a humanized immunoglobulin G Type 2 (IgG_2) monoclonal antibody, derived from a murine precursor by grafting the murine complementarity determining regions onto a human antibody framework, followed by extensive site-directed mutagenesis using proprietary technology to improve binding affinity and specificity. A mutation was performed in the Fc portion of the antibody to decrease its ability to activate complement or to support antibody dependent cell-mediated cytotoxicity.[13,14]

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.[21]

1.2.3. Chronic Low Back Pain

Chronic low back pain, generally defined as back pain that persists more than 12 weeks, represents a significant cause of morbidity, disability, and lost productivity world-wide.[25] Estimates of the prevalence of chronic low back pain vary by study and by geographic region, but chronic low back pain is a common cause of chronic pain and disability in all regions studied. In the United States, the prevalence of chronic low back pain derived from the 1988 United States National Health Interview Survey was 6.4%[27] and a recent survey in 2008 estimated the prevalence of chronic low back pain to be 8.1%.[28] Estimates in Europe suggest that the prevalence of non-specific chronic low back pain is 23%; with 11-12% of the population being disabled by low back pain.[29] In Japan, a large population-based survey found that 3.87% of the population had experienced chronic, disabling low back pain during their lifetime.[30]

The majority of chronic low back pain cannot be attributed to a single pathophysiological or anatomical cause but is usually multifactorial in nature. This back pain is often called "mechanical" or "non-specific" low back pain.[26] Back pain may originate from many spinal structures including facet joints, ligaments, paravertebral musculature, intervertebral discs, and nerves. Common causes of low back pain include injuries to the musculoligamentous structures, age-related degenerative processes of the discs and facet joints, spinal stenosis, and disc herniation.[26] Given the lack of a specific etiology in most cases, therapeutic measures are aimed at providing symptomatic relief and restoring function.

Pharmacological agents commonly used to treat chronic low back pain include nonsteroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressants, muscle relaxants, opioid analgesics, and other drugs active in the central nervous system. However, these agents are not fully effective in many patients, and the use of these agents can be limited by side effects such as gastrointestinal bleeding, somnolence and cognitive impairment. There are, in addition, a variety of other care modalities, such as epidural injections, nerve blocks, facet joint injections, implanted electrical stimulators and pumps, physical therapy, chiropractic and acupuncture, which are expensive and unproven and still leave many patients with inadequate pain relief. Pharmacologic management of pain not responsive to NSAIDs without the toxicities of opiates is needed for patients experiencing moderate-to-severe chronic low back pain.

1.2.4. Overview of Clinical Studies

A total of 32 clinical studies involving over 11,000 patients have been conducted with tanezumab 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.

A total of 17 clinical studies overall (4 Phase 2 studies and 13 Phase 3 studies), were initiated to provide evidence of efficacy and safety of tanezumab with intravenous (IV) or subcutaneous (SC) administration for the relief of the signs and symptoms of osteoarthritis alone or in combination with 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.

The efficacy and safety of tanezumab IV in chronic low back pain has been evaluated in 3 Phase 2 studies (N=1564). The first was a small Phase 2 proof-of-concept study (A4091004;[16] N=217) which evaluated the efficacy and safety of tanezumab 200 µg/kg IV relative to placebo or naproxen 500 mg twice a day (BID). This study was followed by a Phase 2 dose-ranging study (A4091012;[17] N=1347) that evaluated the efficacy and safety of fixed doses of tanezumab of 5 mg, 10 mg, and 20 mg IV relative to placebo or naproxen 500 mg BID and a long term safety extension study (A4091039;[18] N=848) which evaluated the safety and efficacy of tanezumab 10 mg and 20 mg IV and SC administered every 8 weeks for 56 weeks.

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 two Phase 2 studies in metastatic bone pain have been conducted. 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.[1] On March 12, 2012, the FDA Arthritis Advisory Committee reviewed these results as well as those prepared by the FDA.[2,3] 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).

In animal studies in rats and non-human primates (described in Section 5.3 of the tanezumab Investigators' Brochure), 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 function study in non-human primates (described in Section 5.1 of the tanezumab Investigators' Brochure), functional changes in the cardiovascular system controlled by the sympathetic nervous system were not observed.

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.

1.2.4.1. Efficacy of Tanezumab in the Treatment of Chronic Low Back Pain

The efficacy of tanezumab in chronic low back pain has been evaluated in a double-blind, randomized, placebo- and active -controlled Phase 2 study (A4091012).[17]

Study A4091012 evaluated the efficacy and safety of multiple doses of tanezumab 5 mg, 10 mg, or 20 mg administered IV every 8 weeks compared to placebo or naproxen 500 mg BID in treating subjects with chronic low back pain. The primary endpoint of the study was the mean change in the daily average Low Back Pain Intensity score from Baseline to Week 16 with Baseline Observation Carried Forward (BOCF) imputation. Key secondary efficacy endpoints were the Roland Morris Disability Questionnaire (a measure of function used for low back pain) and Patient Global Assessment of Low Back Pain.

A total of 1347 subjects were randomized and treated and by definition comprised the ITT cohort in the study. The mean age of the study population was approximately 52 years (range 18-89 years). There was a small majority of women (53%) who participated and the average duration of chronic low back pain was approximately 11 years.

Tanezumab 10 mg and 20 mg provided significant improvement across the pain, function, and global efficacy domains at Week 16 compared to both placebo and naproxen treatment. The magnitude of efficacy was similar between these tanezumab doses. The observed treatment differences between tanezumab 5 mg and placebo treatment reached statistical significance for only one of three primary measures of efficacy. Naproxen treatment was associated with a significant reduction in pain versus placebo treatment.

Statistically significant response rates compared to placebo treatment were demonstrated at Week 16 with tanezumab 10 mg and 20 mg for the percentage of subjects with reductions in pain ≥30%, ≥50%, ≥70%, and ≥90% in the Low Back Pain Intensity efficacy measure. Tanezumab 20 mg was statistically superior to naproxen treatment at the ≥30% and ≥50% response levels and tanezumab 10 mg was superior to naproxen treatment at the ≥70% and ≥90% response levels. The percent of subjects with ≥30% and ≥50% reductions in pain were significantly greater with tanezumab 5 mg and naproxen treatment as compared to placebo- treated subjects.

1.2.4.2. 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 1 are considered to be expected in subjects who are treated with tanezumab.

Table 1. Adverse Drug Reactions in Subjects All Subjects Receiving Tanezumab

System Organ Class	Adverse Drug Reaction	Frequency[2]
Nervous system disorders	Burning sensation Carpal tunnel syndrome Hyperesthesia Hypoesthesia Paraesthesia	Common
	Allodynia Neuropathy peripheral	Uncommon
Musculoskeletal and connective tissue disorders	Rapidly Progressive Osteoarthritis *(in patients with underlying osteoarthritis[1])*	Uncommon
	Arthralgia Joint swelling Myalgia Pain in extremity	Common
General disorders and administration site conditions	Oedema peripheral	Common

[1] 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.
[2] Common (≥1% and <10%); Uncommon (≥0.1% and <1%).

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

A total of 7491 subjects were treated in 9 controlled Phase 3 osteoarthritis studies. The majority of these subjects were treated in studies using IV administration of tanezumab; however, N=985 subjects with osteoarthritis were treated in 2 studies using SC administration. The adverse event profile of SC administration of tanezumab is comparable to the IV route. 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.

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.

The most common adverse events reported in the non-controlled, long-term Phase 3 osteoarthritis studies were similar to those seen in the controlled Phase 3 osteoarthritis studies with the exception of the inclusion of musculoskeletal pain and exclusion of hypertension and nasopharyngitis and all gastrointestinal-related adverse events. Dose-related increases in the incidence of peripheral edema, joint swelling, osteoarthritis and paresthesia were observed.

In general, the adverse event profile observed in subjects with chronic low back pain is similar to that observed in the osteoarthritis patient population. The tanezumab 10 mg treatment had a better tolerability profile than the tanezumab 20 mg treatment. The tanezumab 20 mg treatment group had a higher overall incidence of adverse events, a higher incidence of severe adverse events, and a higher incidence of subjects who withdrew due to an adverse event. There were no investigator reports of osteonecrosis or total joint replacements in Study A4091012. In Study A4091039, there was one event of rapidly progressive osteoarthritis in a chronic low back pain subject treated with tanezumab 20 mg who had severe osteoarthritis in the affected knee prior to study entry.

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 replacements, the risk of rapidly progressive osteoarthritis with tanezumab treatment is greater than with placebo or active comparator treatment.

1.2.4.3. Sympathetic Nervous System

In completed Phase 3 osteoarthritis studies, the incidence and discontinuation rates due to adverse events consistent with decreased sympathetic function associated with tanezumab monotherapy (combined doses of 2.5 to 10 mg) were less than or equal to rates with placebo or active comparator. No evidence of dose related elevations in the frequency of adverse events suggestive of decreased sympathetic nervous system function were observed at tanezumab doses of 2.5 to 10 mg in subjects with osteoarthritis or chronic low back pain. Tanezumab 20 mg in chronic low back pain had marginally higher event rates compared to placebo and active comparator treatment groups.

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, the data are not suggestive of an adverse effect of tanezumab on autonomic function.

1.2.4.4. Subcutaneous Administration of Tanezumab in Clinical Studies

The formulation of the tanezumab drug product for SC injection is identical to that used for IV administration and is administered as a 1 mL SC injection in the thigh or abdomen. The safety and efficacy of tanezumab when administered by SC injection has been evaluated in OA subjects primarily in two studies, A4091027 and A4091043, and in subjects with chronic low back pain in one study (A4091039), all of which were impacted by the FDA-imposed clinical hold.[18,19,20] A total of 1905 subjects were treated in these studies. The observed efficacy and safety profile of tanezumab administered SC was similar to IV administration.

In Study A4091039, tanezumab was planned to be administered IV every 8 weeks for 3 administrations followed by SC every 8 weeks for 4 administrations. A total of 848 subjects were treated with tanezumab in this study of which of 240 (28%) received ≥1 dose of SC tanezumab. The planned duration of the study was 64 weeks; however, due to the FDA-imposed clinical hold, the majority of the subjects received only 1 dose of SC tanezumab. SC administration of tanezumab was well tolerated in this study and provided durable pain relief, improvement in physical functioning and Patient's Global Assessment of Low Back Pain. All injection site reactions were mild in severity and the proportion of subjects who experienced injection site reactions was similar between treatment groups.

In Studies A4091027[19] and A4091043,[20] the overall incidence of adverse events with tanezumab administered SC 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 incidence of SC injection site reactions was generally low (ranging from 1.4% to 4.7% in the tanezumab SC treatment groups) and comparable to the placebo (2.8%) and the tanezumab 10 mg IV (3.6%) treatment groups. The higher incidence of adverse events of injection-site reaction compared to other studies was likely due to the implementation of directed injection-site assessments – a procedure that was not a component of earlier tanezumab studies, which had included only IV administration of tanezumab. The frequency of injection site reactions with SC tanezumab treatment was similar to the SC placebo treatment group and 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.

1.2.4.5. 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. These data were 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.[1]

After careful investigation no evidence was found to indicate 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.

Risk mitigation measures have been developed as an outgrowth of the joint-related safety analyses to reduce the risk of rapidly progressive osteoarthritis. 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. These risk mitigation measures have been included in the tanezumab clinical development program and those applicable to this study and 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 osteoarthritis of the knees and hips as defined by American College of Rheumatology clinical and radiographic criteria, subjects with Kellgren Lawrence Grade 2 or greater hip osteoarthritis, subjects with Kellgren Lawrence Grade 3 or greater knee osteoarthritis, and subjects with evidence of shoulder osteoarthritis (as determined by the presence of symptoms and radiologic findings consistent with osteoarthritis), (4) exclude subjects with evidence of rapidly progressive osteoarthritis or risk factors for such from participating in clinical studies, (5) discontinue treatment with study medication in subjects who fail to achieve adequate pain relief and (6) 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 and protocol-level stopping rules.

Risk Characterization: (1) Comprehensive evaluation of osteoarthritis medical history prior to study entry, (2) scheduled radiographic assessments during the studies, (3) surgical and post-operative total joint replacement outcomes, and (4) biomarker determinations.

1.2.5. Dose Selection Rationale

Intravenous administration of tanezumab at doses of 5 mg, 10 mg, and 20 mg was shown to reduce pain and improve function in a dose-related manner in the chronic low back pain study A4091012. Both the tanezumab 10 mg and 20 mg doses demonstrated superior efficacy compared to placebo and to naproxen. There was little incremental benefit in efficacy with tanezumab 20 mg treatment compared to tanezumab 10 mg. The tanezumab

5 mg dose did not achieve statistically significant superiority versus placebo in the primary endpoint of pain or the key secondary endpoint of function at Week 16 although significant differences versus placebo were observed at interim timepoints up to Week 12 and the overall efficacy profile of tanezumab 5 mg was similar to naproxen.

In contrast to the efficacy data, tanezumab 10 mg had a better safety profile compared with tanezumab 20 mg treatment. As one of the risk mitigation features identified through analysis of orthopedic safety and efficacy data, no further study of the tanezumab 20 mg dose will be conducted in subjects with chronic low back pain as this dose did not provide sufficient additional efficacy benefit over the 10 mg dose.

This study will investigate the efficacy and safety of a fixed dose of tanezumab 5 mg and 10 mg administered SC seven times at 8-week intervals. This study will provide additional experience with the tanezumab 5 mg and 10 mg doses which have been shown to provide efficacy benefits with a favorable safety profile in a previous Phase 2 clinical trial. In addition, the study will evaluate the long term safety profile of tanezumab treatment for chronic low back pain compared to tramadol PR, a medication commonly utilized for the treatment of chronic low back pain.

1.2.6. Rationale for Placebo Treatment

This study has a placebo comparator group for the first 16 weeks of the Treatment Period. The use of a placebo comparator is the gold-standard for assessing efficacy in short-term chronic low back pain studies. This is particularly relevant considering that the intended subject population for this study consists of subjects who have had inadequate pain relief with pharmacologic treatments commonly used in chronic low back pain or are unable to take these medications due to contraindication or inability to tolerate them. Utilization of placebo as a comparator also necessitates a smaller sample size thus demonstrating the study objectives of efficacy more efficiently than in an active comparator alone study. In addition, the use of a placebo arm is most important when the trial endpoints are subjective measures such as those used in this study, because of the variation in the way individuals perceive patient-reported outcomes. This was reported to be particularly relevant for studies involving pain relief, depression, and asthma.[31] Rescue medication (acetaminophen/paracetamol) will be provided to all subjects for use in the event of inadequate pain relief throughout the Treatment Period. To minimize the duration of placebo treatment, subjects who are randomized to the placebo treatment group will be switched in a blinded manner to tanezumab after the primary efficacy assessment at Week 16.

1.2.7. Rationale for Tramadol as an Active Comparator

Tramadol is a synthetic, centrally-acting analgesic that acts as a weak μ-opioid receptor agonist and as an inhibitor of both norepinephrine and serotonin neuronal reuptake. For most patients, first line medication options for chronic low back pain are NSAIDs and acetaminophen/paracetamol. Tramadol is a therapeutic option for the long-term treatment of chronic low back pain in patients whose pain is not controlled by acetaminophen/paracetamol or NSAIDs.[34] Tramadol PR (marketed as Tradorec® XL in the United Kingdon [UK] and Europe), is a prolonged-release (PR) formulation of tramadol intended for once daily dosing. Common (≥10% of subjects) adverse drug reactions observed with tramadol PR doses of ≤300 mg per day include dizziness, nausea, constipation, and headache.

Subjects randomized to the tramadol PR arm will initiate tramadol at the recommended starting dose for moderate-to-severe pain per the prescribing information and may increase the dose to the maximum recommended daily dose.

1.2.8. Benefit vs Risk for the Study Population

The population selected for this study is subjects with moderate to severe chronic low back pain who have had inadequate pain relief with most conventional pharmacological treatment options for low back pain or who are unable to take these medications due to a contraindication or the inability to tolerate them and who are seeking effective treatment options. The rationale for the choice of this population is to optimize the potential benefit:risk relationship for subjects entering the study by selecting subjects who have pain that is more severe or treatment resistant and who have limited treatment options remaining.

In order to reduce risk in this population, the tanezumab doses tested in this study will be limited to tanezumab 5 mg and 10 mg. Subjects with symptomatic osteoarthritis of the knees, hips or shoulders (as defined by American College of Rheumatology clinical and radiographic criteria) and subjects with Kellgren Lawrence Grade 2 or greater hip osteoarthritis, or Kellgren Lawrence Grade 3 or greater knee osteoarthritis will be excluded from participation. Additional risk mitigation measures have been developed as an outgrowth of the joint-related safety analyses to reduce the risk of rapidly progressive osteoarthritis and are included in this study.

Complete information for tanezumab may be found in the Single Reference Safety Document, which for this study is the Investigator's Brochure. The Single Reference Safety Document for tramadol PR is the Endo Ventures Limited UK Summary of Product Characteristics..

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

- Demonstrate superior analgesic efficacy of tanezumab 10 mg and 5 mg administered subcutaneously (SC) every 8 weeks compared to placebo at Week 16.

2.1.2. Secondary Objectives

- Evaluate the long-term safety of tanezumab 10 mg and 5 mg SC administered every 8 weeks (7 administrations);
- Estimate the long-term analgesic efficacy of tanezumab 10 mg and 5 mg SC administered every 8 weeks (7 administrations) up to Week 56;
- Compare the analgesic efficacy of tanezumab 10 mg SC administered every 8 weeks relative to an active comparator (oral tramadol PR) at Week 16.

2.2. Endpoints

2.2.1. Primary Endpoint

- Change from Baseline to Week 16 in the daily average Low Back Pain Intensity (LBPI) score as measured by an 11-point Numeric Rating Scale for tanezumab vs placebo.

2.2.2. Key Secondary Endpoints

- Change from Baseline to Week 16 in the Roland Morris Disability Questionnaire (RMDQ) for tanezumab vs placebo;

- Change from Baseline to Week 16 in the daily average LBPI score as measured by an 11-point Numeric Rating Scale for tanezumab vs tramadol PR.

2.2.3. Secondary Endpoints

Efficacy-Related Endpoints:

- Change from Baseline to Weeks 2, 4, 8, 12, 24, 32, 40, 48, 56, and 64 in average LBPI score;

- Change from Baseline to Weeks 2, 4, 8, 16 (for tanezumab vs tramadol) 24, 32, 40, 48, 56, 64 and 80 in RMDQ total score;

- Change from Baseline to Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, and 64 in Patient's Global Assessment of Low Back Pain;

- Cumulative distribution of percent change from Baseline in average LBPI score to Weeks 16, 24, and 56 (endpoint for summary only);

- Response as defined by a ≥30%, ≥50%, ≥70% and a ≥90% reduction from Baseline in daily average LBPI score derived from the subject diary at Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, 56, and 64;

- Response as defined by a ≥30%, ≥50%, ≥70% and a ≥90% reduction from Baseline in the RMDQ score at Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, 64 and 80;

- Cumulative distribution of percent change from Baseline in RMDQ score to Weeks 16, 24, and 56 (endpoint for summary only);

- Change from Baseline to Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, and 64 in the Brief Pain Inventory-short form (BPI-sf) scores for Worst Pain, Average Pain, Pain Interference Index (composite function score), Pain Interference with General Activity, Pain Interference with Walking Ability, Pain Interference with Sleep, and Pain Interference with Normal Work;

- Chronic Low Back Pain Responder Index analysis [composite endpoint of average LBPI score, Patient's Global Assessment of Low Back Pain, and RMDQ total score at Weeks 2, 4, 8 16, 24, 32, 40, 48 and 56;

- Treatment Response: Improvement of ≥2 points in Patient's Global Assessment of Low Back Pain at Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, and 64;

- Euro Quality of Life Health State Profile (EQ-5D-5L™) dimensions and overall health utility score at Baseline, Weeks 8, 16, 24, 40, 56, and 64;

- Work Productivity and Activity Impairment Questionnaire: Low Back Pain (WPAI:LBP) change from Baseline to Weeks 16, 56, and 64, in the percent work time missed due to chronic low back pain, percent impairment while working due to chronic low back pain, percent overall work impairment due to chronic low back pain, and percent activity impairment due to chronic low back pain;

- Incidence of and time to discontinuation due to lack of efficacy;

- Usage of rescue medication (incidence, and number of days of usage) during Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, 56 and Week 64;

- Usage of rescue medication (amount taken) during Weeks 2, 4, 8, 12 and 16;

- Health Care Resource Utilization at Baseline, and Weeks 64, and 80.

Treatment Satisfaction Measures:

- Treatment Satisfaction Questionnaire for Medication v.II (TSQM) score at Weeks 16 and 56;

- Patient Reported Treatment Impact Assessment-Modified (mPRTI) at Weeks 16 and 56.

Safety Measures:

- Adverse events;

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

- Orthostatic (supine/standing) blood pressure assessments;

- Survey of Autonomic Symptoms scores;

- Joint safety adjudication outcomes;

- Total joint replacements;

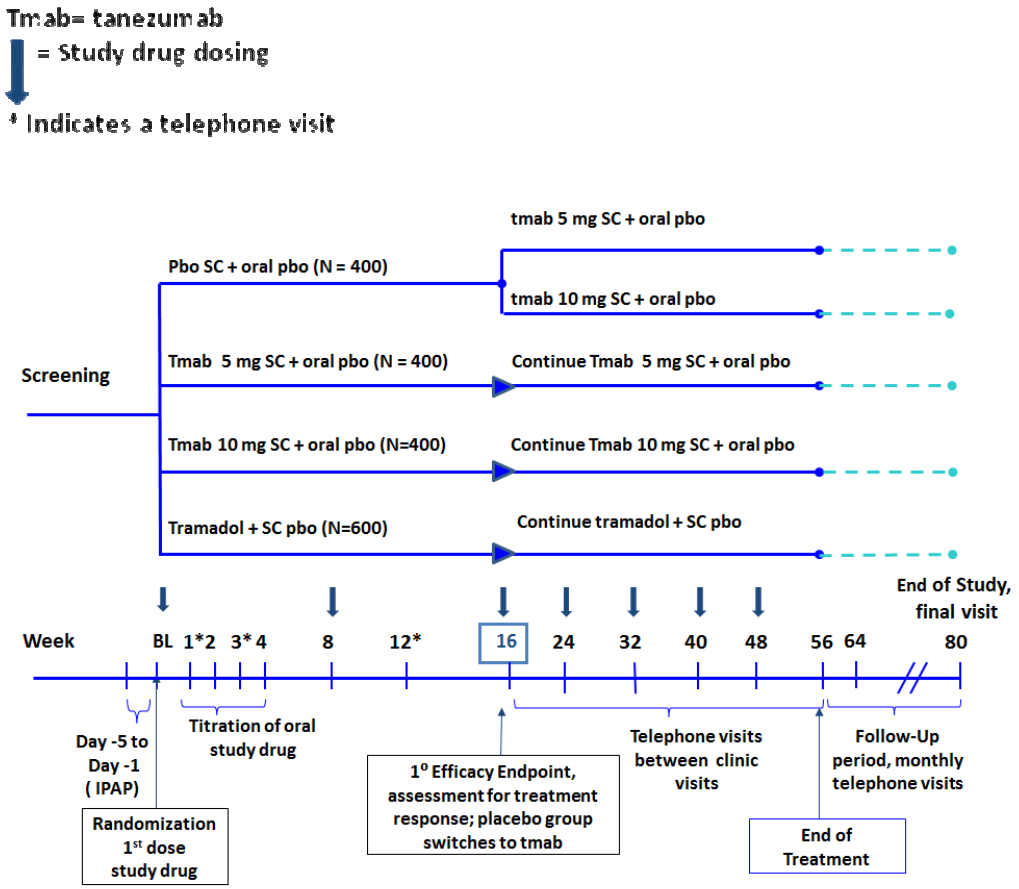
- Neurologic examination (Neuropathy Impairment Score [NIS]);
- Anti-drug antibody assessments (ADA);
- Physical examinations.

2.2.4. Tertiary Endpoints

- Plasma tanezumab concentrations;
- Serum NGF assessments;
- Serum and urine osteoarthritis biomarker concentrations;
- NIH Pain Consortium Chronic Low Back Pain Minimum Dataset at Baseline, Weeks 16 and 56.

3. STUDY DESIGN

Figure 1. Study Schematic



This is a randomized, double-blind, placebo- and active-controlled, multicenter, parallel-group Phase 3 study of the efficacy and safety of tanezumab when administered by SC injection for up to 56 weeks in subjects with chronic low back pain. Approximately 1800 subjects will be randomized to 1 of 4 treatment groups in a 2:2:2:3 ratio (ie, 400 subjects per treatment group for the placebo, tanezumab 5 mg and tanezumab 10 mg treatment groups and 600 subjects in the tramadol PR treatment group). Treatment groups will include:

1. Placebo administered SC at an 8-week interval plus placebo matching tramadol PR up to Week 16. At the Week 16 visit, subjects in this group who meet the efficacy responder criteria described in Section 6.9.1 will be switched in a blinded fashion in a 1:1 ratio to either tanezumab 5 mg or tanezumab 10 mg administered SC at an 8 week interval plus placebo matching tramadol PR to Week 56;

2. Tanezumab 5 mg SC administered at an 8-week interval plus placebo matching tramadol PR to Week 56;

3. Tanezumab 10 mg SC administered at an 8-week interval plus placebo matching tramadol PR to Week 56;

4. Oral tramadol PR plus placebo administered SC at an 8-week interval to Week 56.

The study is designed with a total duration (post-randomization) of up to 80 weeks and will consist of three periods: Screening (up to a maximum of 37 days; includes a Washout Period and an Initial Pain Assessment Period), a Double-blind Treatment Period (comprised of a 16-week Primary Efficacy Phase and a 40-week Long Term Safety and Efficacy Phase), and a Follow-up Period (24 weeks). The Screening Period (beginning up to 37 days prior to Randomization) includes a Washout Period (lasting 2-32 days), if required, and an Initial Pain Assessment Period (the 5 days prior to Randomization/Baseline).

Prior to entering the study, subjects must have a documented history of previous inadequate treatment response to medications in 3 different categories of agents commonly used to treat and generally considered effective for the treatment of chronic low back pain. (See Inclusion Criterion #5).

3.1. Screening

After obtaining informed consent at Screening, the investigator will evaluate the subject based upon the Screening inclusion/exclusion criteria. The Screening Period will include the discontinuation and washout of all prohibited pain medications, X-rays to confirm the subject's radiographic eligibility for the study, and the Initial Pain Assessment Period (IPAP). The allowed duration for Screening is 37 days, which includes the Washout Period and the 5 day Initial Pain Assessment Period. Subjects who meet eligibility criteria at the Screening visit will be instructed in the completion of an electronic diary which will use Interactive Response Technology (IRT). The subject will record LBPI scores, joint pain scores, NSAID and rescue medication usage via the IRT. During the Screening Period, all subjects will undergo X-rays of the hips, knees and shoulders. 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, ankles and excluding the joints of the toes and hands. All X-rays will be assessed by a Central Reader to determine the radiographic eligibility of subjects for study participation. It is recommended that the radiographs required at Screening be obtained at least two weeks prior to the Baseline visit to permit Central Reader review of the images and to establish subject eligibility for initial dosing in the study. At Screening, subjects will also provide a pain score (scored with an 11-point numerical rating scale [NRS]) for both knees, hips, and shoulders and any other major joint for which a radiograph is obtained (see Section 7.3.2).

The minimum washout period is 2 days (48 hours) for all prohibited medications that have an elimination half-life of less than 10 hours or at least 5 times the elimination half-life for those medications with longer half lives. Subjects who do not require a washout of prohibited pain medications may begin the Initial Pain Assessment Period the day after X-ray confirmation of radiographic eligibility has been received from the Central Reader.

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

The Initial Pain Assessment Period includes the 5 days prior to the Randomization/Baseline visit. During this period, the daily average LBPI score measured by an 11-point Numeric Rating Scale will be collected via Interactive Response Technology (IRT).

On a weekly basis beginning at the Initial Pain Assessment Period and through Week 80 of the study, the subject will be asked via IRT if he/she has experienced new or increased pain in a major joint (refer to Section 7.3.2). If a subject responds that he/she has experienced new or increased pain in a major joint (post-baseline), the subject will be asked to rate his/her pain in that joint on a 11-point numeric rating scale, using a 24-hour recall and will be asked to rate his/her pain in that joint for the remainder of the study. Subjects with severe, persistent joint pain will have more detailed evaluations to investigate the pain (See Section 7.4.4).

3.2. Treatment Period (Baseline to Week 56)

Those subjects who are eligible at the Baseline visit (Day 1) will be randomized to 1 of the 4 treatment groups.

Administration of SC study medication (placebo, tanezumab 5 mg or tanezumab 10 mg) will occur at Baseline and Week 8. Assuming a sufficient treatment response is demonstrated at Week 16, (see next paragraph) additional administration of SC study medication will occur at Weeks 16, 24, 32, 40 and 48. Subjects will be observed for adverse events including signs and symptoms of hypersensitivity in the clinic for a minimum of 1 hour after each administration of SC study drug.

At the Week 16 visit, subjects must have at least a 30% reduction in average LBPI score relative to Baseline and at least a 15% reduction in average LBPI score relative to Baseline at any week from Week 1 to Week 15 in order to continue study treatment to Week 32. At the Week 32 visit, all subjects must have at least a 30% reduction in average LBPI score relative to Baseline in order to continue study treatment to Week 56. Subjects who do not meet these response criteria will be discontinued from the Treatment Period and enter the Early Termination Follow-up Period (See Section 6.20.1).

Each treatment group will receive tramadol PR or matching placebo tablets to maintain blinding of the active oral study medication. At Baseline, subjects randomized to tramadol PR will be started on a tramadol PR dose of 100 mg once a day (QD). During the first 4 weeks of the treatment period (Baseline to Week 4), the tramadol PR dose may be adjusted as necessary every 5 to 7 days by 100 mg increments depending on pain relief or tolerability up to a maximum dose of tramadol PR 300 mg QD. In order to maintain the blind, subjects receiving matching placebo will also be allowed to titrate their dose. Study staff should contact subjects by telephone at Weeks 1 and 3 to evaluate pain relief and tolerability of the oral study medication and to counsel the subject regarding dose adjustment. There will be an in-clinic visit at Week 2. Subjects should be instructed that all dose escalations or reductions should be made only after consultation with the study site staff at a clinic visit or via telephone contact. After the Week 4 visit, the dose of tramadol PR (or matching placebo) should be held constant until the Week 56 visit. *Note: For subjects participating in Europe, following the completion of the Week 16 visit through the Week 56 visit, the dose of tramadol PR or oral placebo may be decreased to a minimum of 100 mg per day, if clinically indicated. If the dose of tramadol PR or oral placebo is reduced, it may later be re-escalated for reasons of inadequate pain control to a maximum of the previous individually titrated dose (See Section 5.5.2).*

Oral study medication and rescue medication will be dispensed at every clinic visit beginning at the Baseline visit and concluding with the Week 48 visit. Oral tramadol PR or matching placebo will be self administered by subjects on a daily basis from Baseline through Week 56.

At the Week 16 visit, presuming a treatment response is demonstrated; subjects randomized to the placebo treatment arm will be switched in a blinded manner to tanezumab SC treatment. These subjects will be switched in a 1:1 ratio to tanezumab 5 mg or tanezumab 10 mg SC plus matching placebo and will receive the first administration of SC tanezumab at Week 16.

The Primary Efficacy Phase will comprise the time from Baseline to Week 16. The primary efficacy endpoint, average LPBI score, will be collected daily via IRT from Baseline to Week 16. Rescue medication use will be recorded daily and NSAID use and joint pain assessments will be recorded once a week via the IRT. Secondary efficacy and safety assessments will be collected at study visits at Weeks 2, 4, 8, and 16. During the Primary Efficacy Phase, all concomitant medications for the treatment of chronic low back pain are prohibited with the exception of rescue medication (acetaminophen/paracetamol) and study medication. During the Primary Efficacy Phase, subjects are permitted to continue with

stable non-pharmacologic treatments (eg, massage, physical therapy) for chronic low back pain, but are prohibited from beginning new non-pharmacological treatments until after Week 16.

The Long Term Safety and Efficacy Phase will begin after the Week 16 visit and continues until Week 56. The average LBPI score, rescue medication use, NSAID use, and joint pain assessments will be collected once a week via IRT, and safety and secondary efficacy assessments will be collected at study visits at Weeks 24, 32, 40, 48 and 56. In addition, subjects will be contacted by telephone at Weeks 20, 28, 36, 44, and 52 to assess compliance and collect adverse event, concomitant drug and concomitant non-drug information. Starting at Week 16, at the discretion of the investigator, subjects may begin certain permitted medications and non-pharmacological therapies for the treatment of low back pain (See Section 5.8.2). X rays of the hips, knees, and shoulders as well as any additional joint that was imaged at Screening or identified as at risk (See Section 7.4.4) during the study will be obtained for all subjects at Weeks 24 and 56. These images will be sent to the Central Reader for review. At Week 24, confirmation of the continuing radiographic eligibility of the subject must be received from the Central Reader prior to administration of the Week 24 SC study medication.

3.3. Follow up Period (After Week 56 to Week 80)

3.3.1. Follow-up Period

Subjects who complete the Week 56 visit will be considered to have completed the Double-blind Treatment period and will enter the 24-week Safety Follow-up period. Subjects that have completed the Double-blind Treatment period and have entered the 24-week Safety Follow-up period and complete the Week 80 visit will be considered to have completed the study. Subjects who discontinue study treatment prior to completing the Week 56 visit will not be considered to have completed the Double-blind Treatment Period. Subjects that do not complete the Double-blind Treatment period but who enter and complete the 24-week Early-termination follow-up period will be considered to have completed the study while those subjects who do not complete the 24-week Early-termination follow-up period will not be considered to have completed the study.

With the completion of the Week 56 visit, the subjects will begin the 24-week Follow-up Period and will be asked to return to the clinic for 2 additional study visits.

At Week 64 (16 weeks after the last dose of SC study medication) efficacy assessments, adverse event and concomitant medication information will be collected and standard of care medication will be initiated if determined appropriate by the Investigator. Standard of care treatment refers to approved treatments generally considered to be effective and in common use for the treatment of chronic low back pain (See Section 5.8.2, for details of standard of care treatment). Between the clinic visits in the Follow-up Period, subjects will be contacted by telephone by clinical research site staff at Weeks 60, 68, 72, and 76 to collect adverse event, concomitant drug and concomitant non-drug information. The average LBPI score will be collected once a week (using a 24 hour recall period) through the Week 64 visit via IRT. Subjects will continue to report new or increased joint pain, acetaminophen, and

NSAID use on a weekly basis via IRT through Week 80. As in the Double-blind Treatment Period, subjects with severe, persistent joint pain will have more detailed evaluations to investigate the pain. At the end of the 24-week Follow-up period, subjects will return for a final study visit at Week 80 (End of Study). At that visit, all End of Study procedures are to be completed including X-rays of the hips, knees and shoulders as well as any additional joint that was imaged at Screening or identified as at risk during the study. The window for the Week 80 X-rays is ±30 days of the nominal time of the visit but should be obtained as close as possible to the Week 80 visit, and preferably no more than 14 days after the Week 80 visit.

4. SUBJECT SELECTION

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

4.1. Inclusion Criteria

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

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

1. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative) has been informed of all pertinent aspects of the study.
2. Male or female of any race, ≥18 years of age.
3. Presents with duration of chronic low back pain of ≥3 months.
4. Primary location of low back pain must be between the 12th thoracic vertebra and the lower gluteal folds, with or without radiation into the posterior thigh, classified as Category 1 or 2 according to the classification of the Quebec Task Force in Spinal Disorders (Appendix 1).
5. Documented history of previous inadequate treatment response (ie, the agent has not provided sufficient pain relief while on the maximum tolerated dose of the therapy or the subject is unable to take the agent due to contraindication or inability to tolerate) to at least 3 different categories of agents commonly used (from the list in Table 2) and generally considered effective for the treatment of chronic low back pain. If a subject has been treated with 2 or more agents simultaneously but continued to have inadequate pain relief, the pain would be considered unresponsive to all of the agents taken.

Table 2. Medication Categories Commonly Utilized or Considered Effective for Chronic Low Back Pain

- Acetaminophen/paracetamol or low dose NSAIDs (ie, non-prescription NSAIDs taken at the labeled non-prescription dose)
- Prescription NSAIDs or coxibs
- Opioids*
- Tapentadol
- Tricyclic antidepressants
- Benzodiazepines or skeletal muscle relaxants
- Lidocaine patch
- Duloxetine or other serotonin-norepinephrine reuptake inhibitors

*For protocol-qualifying purposes, tramadol is not considered part of the opioid category.

6. LBPI score of ≥5 at Screening.

7. Completes at least 4 daily pain diaries during the 5 days prior to the day of Randomization, with an average LBPI score of ≥5.

8. Patient's Global Assessment of Low Back Pain must be "fair", "poor" or "very poor" at Baseline.

9. Subjects must be willing to discontinue all pain medications for chronic low back pain except rescue medication and study medication and not use prohibited pain medications throughout the duration of the study except as permitted per Protocol.

10. Female subjects of childbearing potential and at risk for pregnancy must agree to use 2 highly effective methods of contraception throughout the study and for 112 days (16 weeks) after the last dose of assigned subcutaneous treatment (See Section 4.4).

11. Female subjects who are not of childbearing potential (ie, meet at least 1 of the following criteria):

    - Have undergone a documented total hysterectomy and/or bilateral oophorectomy;
    - Have medically confirmed ovarian failure;
    - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and confirmed by having a serum follicle stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women.

12. Subjects who are willing and able to comply with lifestyle guidelines, scheduled visits, treatment plan, laboratory tests, and other study procedures through the End of Study visit.

4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

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 ≥45 kg/m^2.

3. Diagnosis of osteoarthritis of the knee or hip as defined by the American College of Rheumatology (ACR) combined clinical and radiographic criteria (Appendix 2); Radiographic criteria will be assessed by the Central Reader.

    - Subjects who have Kellgren Lawrence Grade ≥2 radiographic evidence of hip osteoarthritis will be excluded;

    - Subjects who have Kellgren Lawrence Grade ≥3 radiographic evidence of knee osteoarthritis will be excluded;

    - Subjects who have Kellgren Lawrence Grade ≤2 radiographic evidence of knee osteoarthritis but who do not meet ACR criteria and do not have pain associated with their knee osteoarthritis will be allowed.

4. Subjects with symptoms and radiologic findings (ie, joint space narrowing, osteophytes) consistent with osteoarthritis in the shoulder.

5. History of lumbosacral radiculopathy within the past 2 years, history of spinal stenosis associated with neurological impairment, or history of neurogenic claudication.

6. Back pain due to recent major trauma (eg, vertebral fracture, post-traumatic spondylolisthesis). Subjects with trauma occurring >6 months prior to Screening are eligible to be considered for entry into the study.

7. Current or pending worker's compensation, litigation, disability, or any other monetary settlement regarding his/her chronic low back pain or any other pain condition.

8. Surgical intervention including, but not limited to, procedures such as discectomy, nerve ablation, kyphoplasty, or nucleoplasty during the past 6 months for the treatment of low back pain.

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

10. Fibromyalgia, back pain due to a visceral disorder (eg, endometriosis), or other moderate-to-severe pain that may confound assessments or self-evaluation of the pain associated with chronic low back pain.

11. History of disease that may involve the spine, including inflammatory joint diseases such as seronegative spondyloarthropathy (eg, ankylosing spondylitis), rheumatoid arthritis, infections or tumors of the spinal cord, or Paget's disease of the spine, pelvis or femur.

12. 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; or stress or traumatic fracture.

13. Subjects with radiographic evidence of any one 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 6) pathologic fracture.

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

15. History of significant trauma or surgery to a knee, hip, or shoulder within the previous year.

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

17. Subject considered unfit for surgery, defined as a Grade >3 on the American Society of Anesthesiologists (ASA) physical classification system for surgery (See Appendix 3) or subjects who would not be prepared to undergo joint replacement surgery if required.

18. 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).

19. History of intolerance or hypersensitivity to tramadol or any of its excipients or existence of a medical condition or use of concomitant medication for which the use of tramadol is contraindicated (refer to product labeling).

20. Use of prohibited medications or prohibited non-pharmacological treatments without the appropriate washout period (if applicable) prior to Screening or Initial Pain Assessment Period. Prohibited medications and non-pharmacological treatments and the required washout periods are described in Section 5.8.1.

21. History of known alcohol, analgesic or narcotic abuse within 2 years of Screening.

22. Presence of drugs of abuse (including prescription medications without a valid prescription) or illegal drugs in the urine toxicology screen obtained at Screening.

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

24. 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;
    - New York Heart Association (NYHA) Class III or IV congestive heart failure or known left ventricular dysfunction with ejection fraction ≤35%, cardiomyopathy, myocarditis in the 6 months prior to Screening;
    - Resting tachycardia (heart rate ≥120) or resting bradycardia (heart rate ≤45) on ECG at Screening;
    - QTcF interval >500 msec in the absence of confounding factors like bundle branch block or paced rhythm at Screening;
    - Any other cardiovascular illness that in the opinion of the Investigator would render a subject unsuitable to participate in the study.

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

25. Resting, sitting blood pressure (BP) ≥160 mm Hg in systolic pressure or ≥100 mm Hg in diastolic pressure at Screening. If a subject is found to have untreated significant hypertension at Screening and antihypertensive treatment is initiated, assessment for study eligibility should be deferred until BP and antihypertensive medication have been stable for at least one month. For subjects with previously diagnosed hypertension, antihypertensive medications must be stable for at least 1 month prior to Screening.

26. Subjects who have evidence of orthostatic hypotension based upon replicate orthostatic blood pressure measurements (See Section 7.3.5.1). If orthostatic blood pressure change is not able to be determined (eg, unable to establish a stable supine systolic and diastolic blood pressure), then the subject is not eligible for the study.

27. Subjects with a total impact score of >7 on the Survey of Autonomic Symptoms (See Appendix 14).

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

29. History of cancer within 5 years prior to Screening, except for cutaneous basal cell or squamous cell cancer resolved by excision.

30. Is expected to undergo a therapeutic procedure or to use any analgesic other than those specified in the protocol throughout the pre-treatment and treatment periods that is likely to confound assessment of analgesic efficacy or safety.

31. Previous exposure to exogenous NGF or to an anti-NGF antibody.

32. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3.0 times the upper limit of normal, or creatinine exceeding 1.7 mg/dL (150 μmol/L) in men or 1.5 mg/dL (133 μmol/L) in women, or hemoglobin (Hb) A1c ≥10% at Screening. Repeat confirmatory tests may be performed.

33. Positive Hepatitis B, Hepatitis C, or human immunodeficiency virus (HIV) tests at screening indicative of current infection.

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

    - Alzheimer's disease or other types of dementia;
    - Clinically significant head trauma within the past year;
    - Peripheral or autonomic neuropathy;
    - Multiple sclerosis;
    - Epilepsy or seizure disorder with seizure within the last 2 years;
    - Myopathy.

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

    - Psychotic disorders;
    - Somatoform disorders;
    - Bipolar disorders;
    - Any other psychiatric illness that in the opinion of the Investigator would render a subject unsuitable to participate in the study.

36. Hospital admission for depression or suicide attempt within 5 years of Screening or active, severe major depression at Screening (determined from medical history; if needed, severity of depression may be assessed using the Patient Health Questionnaire [PHQ-9].[23] A score ≥15 on questions 1-9 of the PHQ-9 corresponds to severe depression [See Appendix 5]).

37. Likelihood of being non-compliant with study procedures.

38. Pregnant female subjects; breastfeeding female subjects; female subjects of childbearing potential who are unwilling or unable to use two (2) highly effective methods of contraception as outlined in this protocol for the duration of the study and for 112 days (16 weeks) after last dose of investigational product.

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

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

4.3. Randomization Criteria

At the Baseline/Randomization visit, in addition to meeting all inclusion and exclusion criteria requirements listed above, the following randomization criteria must be met before randomization can be requested from the IRT system at the Baseline visit:

1. Subject must have completed appropriate washout of analgesics.

2. Subject must have entered at least 4 low back pain intensity scores on the daily pain diary in the 5 days prior to the Baseline (Day 1) visit.

3. Subject must have abstained from taking rescue medication (acetaminophen/paracetamol) within the 24 hours that precede dosing.

4. Subjects must meet the Baseline LBPI score and Patient's Global Assessment of Chronic Low Back Pain Baseline requirements (Inclusion Criteria 7 and 8).

5. Review of the ECG and laboratory results and confirmation that there are no clinically significant or exclusionary findings.

6. Radiographic eligibility must have been confirmed by the Central Reader.

4.4. Life Style Guidelines

Subjects should maintain their normal daily routine, including stable doses of permitted medications and exercise program(s). Subjects are also permitted to continue with stable non-pharmacologic treatments (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 Sections 5.8.1 and 5.8.2 for guidance on permitted and prohibited medications and treatments.

Subjects will be advised to avoid elective surgery during the study if possible; the study monitor or Pfizer clinician should be contacted for discussion prior to surgery whenever possible. Subjects who undergo joint replacement or arthroplasty will be discontinued from study treatment and followed as described in 6.20.2.

All female subjects who are of childbearing potential, and are sexually active, 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 SC study medication. The investigator or his/her designee, in consultation with the subject, will confirm the subject has selected the most appropriate methods of contraception for the individual subject from the permitted list of contraception methods (see below), and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for correct use of 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/her designee will instruct the subject to call immediately if the selected contraceptive methods are discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

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

1. Established use of oral, inserted, injected, implanted hormonal or transdermal 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, 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 or 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 study is documented in the study contact list located in the study manual.

To facilitate access to appropriately qualified medical personnel on study related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, subject study number, contact information for the investigational site and contact details for a help desk 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 subject’s participation in the study. The help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems, however it should only be used in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace the established communication pathways between the investigational site and study team for advice on medical questions or problems that may arise during the study. The help desk 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

5.1. Allocation to Treatment

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

Table 3. Study Treatments

Treatment Group	Route of administration	Baseline up to Week 16	Weeks 16 through Week 56
1.) Placebo from Baseline to Week 16; Tanezumab 5 mg or 10 mg from Weeks 16 to 56	SC dosing	Placebo SC	Tanezumab 5 mg or tanezumab 10 mg every 8 weeks
	Oral dosing	Oral placebo dose adjustment Weeks 1-4 followed by stable oral dosing	Placebo stable dosing*
2.) Tanezumab 5 mg + placebo	SC dosing	Tanezumab 5 mg SC every 8 weeks	
	Oral dosing	Oral placebo dose adjustment Weeks 1-4 followed by stable oral dosing	Placebo stable dosing*
3.) Tanezumab 10 mg + placebo	SC dosing	Tanezumab 10 mg SC every 8 weeks	
	Oral dosing	Oral placebo dose adjustment Weeks 1-4 followed by stable oral dosing	Placebo stable dosing*
4.) Tramadol PR + placebo	SC dosing	Placebo SC every 8 weeks	
	Oral dosing	Oral tramadol PR dose adjustment Weeks 1-4 followed by stable oral dosing	Tramadol PR stable dosing*

* For subjects participating in Europe, following the completion of the Week 16 visit through the Week 56 visit, the dose of tramadol PR or oral placebo may be decreased to a minimum of 100 mg per day, if clinically indicated. If the dose of tramadol PR or oral placebo is reduced, it may later be re-escalated for reasons of inadequate pain control to a maximum of the previous individually titrated dose.

The randomization will not be stratified. To achieve the initial randomisation, and re-randomization for placebo patients at Week 16, a blocked static randomization using the ratio 1:1:2:2:3 for placebo→tanezumab 5 mg (at Week 16), placebo→tanezumab 10 mg (at Week 16), tanezumab 5 mg, tanezumab 10 mg, and tramadol will be performed at the beginning of the trial. No active re-randomization will occur at Week 16.

The randomization strategy will result in subjects being randomly assigned in a 2:2:2:3 ratio to the above treatment regimens (Table 3) according to a computer generated randomization code. At Week 16, the subjects who were assigned to placebo at Baseline and who meet the efficacy response criteria (see Section 6.9.1) will be switched in a blinded fashion in a

1:1 ratio to treatment with tanezumab 5 mg or tanezumab 10 mg from Weeks 16 to 56. At the Week 32 visit, subjects must again meet efficacy response criteria (Section 6.13.1) in order to continue study treatment to Week 56. Randomization will be coordinated centrally through 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 securely 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 from the IRT. Further details are provided in the Pharmacy Manual.

5.2. Breaking the Blind

This is a randomized, double-blind, placebo- and active-controlled, 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 should consult with a member of the study team prior to breaking the blind. When the blinding code is broken at the investigator site, the reason must be fully documented and entered on the CRF.

5.3. Subject Compliance

Tanezumab and tramadol PR or corresponding placebo dosing will be recorded on the appropriate CRF. Because tanezumab or corresponding placebo will be administered by site staff subject, compliance with SC treatment is not anticipated to be an issue.

Compliance will be reviewed, and reconciled at each study visit for oral study medication and rescue medication. For oral study treatment (tramadol PR or matching placebo), investigators should encourage subjects to maintain 100% compliance. If a subject's overall compliance with oral study treatment falls to <70% in an 8 week dosing interval, the investigator will counsel the subject on the importance of good compliance and document efforts to improve the subject's compliance.

Refer to Section 5.9 for rules governing rescue medication use.

5.4. Drug Supplies

5.4.1. Dosage Form(s) and Packaging

Tanezumab, placebo for tanezumab, tramadol PR and placebo for tramadol PR will be supplied by the Sponsor or designee.

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.

Tanezumab 10 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 10 mg/mL.

Each vial or prefilled syringe is packed in an individual carton. Each vial or prefilled syringe has a unique container number.

5.4.1.2. Placebo for Tanezumab

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

5.4.1.3. Tramadol PR

Tramadol PR is provided as a tablet containing tramadol 100 mg, tramadol 200 mg and tramadol 300 mg with a prolonged release formulation. The bottles used for the titration period contain 60 tablets of tramadol 100 mg. The bottles for the treatment period contain 72 tablets of tramadol 100 mg or 200 mg or 300 mg. Each bottle has a unique container number.

5.4.1.4. Placebo for Tramadol PR

The placebo for tramadol PR is provided as tablets manufactured by a Pfizer designee to match the active tramadol PR 100 mg, tramadol PR 200 mg and tramadol PR 300 mg respectively. The bottles used for the titration period contain 60 tablets of placebo for tramadol 100 mg. The bottles for the treatment period contain 72 tablets of placebo for tramadol 100 mg or 200 mg or 300 mg. Each bottle has a unique container number.

5.4.1.5. Acetaminophen/paracetamol (Rescue Therapy)

Acetaminophen (paracetamol) caplets/tablets/capsules will be issued by the study sites in its approved marketed product dress (carton, bottle, documents). Any approved commercial product of acetaminophen (paracetamol) tablet/caplet/capsule is permitted.

5.4.2. Preparation and Dispensing

See the Drug Administration Instructions (DAI) for instructions on how to prepare tanezumab 5 mg SC, 10 mg SC and placebo SC for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

5.5. Administration

5.5.1. SC Study Drug Administration

Tanezumab or matching placebo for tanezumab 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 study medication administered as a SC injection. Subcutaneous injections are to be administered in the abdomen or anterior aspect of the thigh. Selection of the SC injection site for each injection will be at the discretion of the Investigator taking into account subject preferences when possible. The SC injection should not be administered in areas where the skin is burned, reddened, inflamed, swollen, or scarred.

5.5.2. Oral Study Drug Administration

Oral tramadol PR or matching placebo will be self-administered by the subject once daily from Baseline through Week 56 (subject to the treatment response requirements described elsewhere). Subjects will swallow the oral study medication whole, and will not manipulate or chew the medication prior to swallowing. Tramadol PR or placebo may be taken without regard to meals, and should be taken whole, at approximately the same time of day.

The dose of the oral tramadol PR or matching placebo may be adjusted from Weeks 1 to 4 (See Section 6.5), according to the subject's pain relief and drug tolerability. Tramadol PR 100 mg tablets will be dispensed at Baseline and Visit 2, and dose increases or dose reductions will be accomplished by adjusting the number of tramadol PR 100 mg tablets or matching placebo tablets taken each day. The dosing frequency may not be adjusted. The maximum daily dose of Tramadol PR is 300 mg per day. If the subject has acceptable toleration of the oral medication without adequate pain control, the dose may be increased. If the subject is having difficulty with toleration of the oral medication, the dose may be reduced. Dose adjustments should be carried out in increments of 100 mg. Determinations of whether to increase or decrease the dose of the oral study medication should be made by medical staff (per local regulations). Dose adjustments may be carried out no more frequently than every 5 days.

At Week 4, the dose of tramadol PR or matching placebo will be fixed at 100 mg, 200 mg or 300 mg per day. Tramadol PR tablets strengths of 100 mg, 200 mg or 300 mg will be dispensed.

For subjects participating in Europe, following the completion of the Week 16 visit through the Week 56 visit, the dose of tramadol PR or oral placebo may be decreased to a minimum of 100 mg per day. Clinical indications for dose reduction include intolerance or decreased low back pain intensity. If the dose of tramadol PR or oral placebo is reduced, it may later be re-escalated for reasons of inadequate pain control to a maximum of the previous individually titrated dose. If subjects continue to have inadequate pain control despite re-escalation, see Sections 5.9 and 5.8.2 for rescue medication and permitted therapies for the treatment of low back pain, respectively.

Dose increases or decreases following the completion of the Week 16 visit through the Week 56 visit will occur at scheduled or unscheduled clinic visits and will be accomplished by changing the dosage strength of the tablets that are dispensed to subjects.

5.6. Drug Storage

Study medication for SC administration (ie, tanezumab or matching placebo) will be shipped and stored at a temperature between 2° and 8°C and protected from light. Study medication for oral administration (ie, tramadol PR or matching placebo) should be stored at temperatures of 15°C to 30°C (59°F to 86°F). Acetaminophen/paracetamol should be stored according to the product's directions.

The Investigator or an approved representative (eg, Pharmacist) will ensure that all investigational product, including any comparative agents and/or marketed productes are stored in a controlled, secure area, with controlled access under recommended storage conditions 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] or Summary of Product Characteristics) will be superseded by the storage conditions stated in the investigational product labeling.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout study. Even for continuous monitoring systems, a log or site procedure which ensures active 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 labeled storage conditions, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. Specific details regarding information the site should report for each excursion will be provided to the site.

5.7. Drug Accountability

The Investigator's site must maintain adequate records documenting the receipt, use, loss, or other disposition of the drug supplies. Subjects should be instructed to bring all untaken oral study medication dispensed at prior visits to each subsequent visit so that compliance can be assessed and drug accountability can be performed by the site.

The sponsor or designee will provide instructions as to disposition of any unused investigational product (eg, at the site).

5.8. Concomitant Medication(s)

5.8.1. Prohibited Medications

5.8.1.1. Medications Prohibited through Week 80

The following medications are prohibited from the time period specified until Week 80 or the final Early Termination Visit.

- Biologics other than study medication (for example: TNF-α inhibitors such as adalimumab, etanercept, infliximab), including any live vaccines, within 3 months of the Initial Pain Assessment Period or during the study. Flumist® Influenza Virus Vaccine Live Intranasal, or other inhaled/intranasal live influenza vaccines (in regions where these vaccines are approved) are the only live attenuated vaccines that will be permitted during the study.
- Systemic corticosteroid therapy within 30 days prior to Screening (inhaled and topical corticosteroids are permitted).
- Local or epidural injection of corticosteroids, as well as injections of corticosteroids in the facet joint or elsewhere in the back within 3 months prior to Screening.

5.8.1.2. Medications Prohibited During Entire Treatment Phase through Week 64

In addition to the prohibited medications listed in Section 5.8.1.1, the following medications are prohibited from the time period specified through Week 64:

- NSAIDs and COX-2 selective inhibitors, both prescription or over-the-counter (OTC) are prohibited beginning 48 hours prior to the start of the Initial Pain Assessment Period (the 5 days prior to Randomization/Baseline) through Week 64 apart from the following circumstances:
  - Limited concomitant use of prescription or OTC NSAIDs may be allowed on an occasional basis for self-limiting conditions not related to chronic low back pain however; they must not be taken within 48 hours of a study visit where efficacy assessments are being collected (from Baseline up to and including the Week 64 visit; for subjects who discontinue, up to Early Termination Visit 2). The study monitor or Pfizer clinician should be contacted for approval prior to use whenever possible, and all doses and days of use must be recorded on the concomitant analgesic CRF. NSAID use should not exceed a total of 80 days between Day 1 (Baseline) and Week 64. Also, since NSAIDs are permitted only to treat self-limiting intercurrent illnesses during the study, the aggregate usage of NSAIDs during any one dosing interval (defined as the period of 8 weeks between 2 SC doses) should not exceed 10 days.

- NSAID usage will be monitored at 2 levels: the cumulative use from Baseline to the subject's current point in the study and the aggregate use during each 8-week dosing interval.

- All subjects who exceed 80 days of cumulative use must be discontinued from treatment and should be entered in the Early Termination Follow-Up period (See Section 6.20.1).

- The number of days of NSAID use will be collected weekly via IRT from Baseline (Day 1) through the Week 80 visit. Additional information regarding NSAID use such as medication names, dosage, and reason for use will be collected by the site via telephone contact or site visits and recorded on a CRF.

- NSAID use during each dosing interval should be closely monitored to detect subjects whose use is not consistent with the treatment of a self-limiting illness or who are demonstrating a pattern of use that would put them at risk of exceeding the cumulative 80 day limit. Subjects taking greater than 10 days of aggregate use of NSAIDs per dosing interval (any dosage of NSAIDs) should be interviewed by study site personnel to determine reason for use and if the subject anticipates being able to take NSAIDs according to protocol requirements in the future. The discussion should be noted in the subject's source documents. Subjects who indicate they are taking NSAIDs because of insufficient chronic low back pain relief or for reasons other than a self-limiting condition or who indicate they cannot or will not follow the protocol-specified requirement for NSAID use should be withdrawn from study treatment and entered in the Early Termination Follow-Up period (See Section 6.20.1). Subjects who exceed the 10-day aggregate limit of NSAIDs for the treatment of self-limiting illnesses should be counseled by the site staff regarding the importance of adhering to these limits. Subjects who indicate that they anticipate being able to take NSAIDs no more than 10 days per dosing interval going forward will be allowed to continue in the treatment period.

- Recurrence of NSAID use exceeding the 10-day aggregate limit of NSAIDs per dosing interval should result, in all but exceptional circumstances, in the subject being withdrawn from study treatment and entered in the Early Termination Follow-Up period (See Section 6.20.1).

- Aspirin at doses >325 mg/day or salicylate containing medications.

- Opioid analgesics are prohibited beginning 48 hours prior to the start of the Initial Pain Assessment Period through Week 64.

5.8.1.3. Prohibited Medications During the Primary Efficacy Phase (through Week 16)

In addition to the prohibited medications listed in Section 5.8.1.1 and Section 5.8.1.2, the following medications are prohibited from Washout through Week 16:

- Analgesics for chronic low back pain by any route (ie, oral, inhaled, topical, injected, rectal) except study medication (tanezumab and tramadol PR) and provided rescue medication (acetaminophen/paracetamol). Use of analgesics except acetaminophen/paracetamol is prohibited beginning 48 hours prior to the start of the Initial Pain Assessment Period (the 5 days prior to Randomization/Baseline) or at the period of time prior to the start of the Initial Pain Assessment Period that is 5 times the half-life of the particular analgesic used, whichever is greater. Refer to Appendix 4: Half-Lives of Prohibited Prior and Concomitant Medications, for a detailed washout schedule for prohibited medications. This is not an exhaustive list and the study monitor or Pfizer clinician 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. Subjects will be counseled to review ingredients of over-the-counter products and to report their use as concomitant medications.

- Muscle relaxants (Refer to Appendix 4) are prohibited beginning 48 hours prior to the start of the Initial Pain Assessment Period (the 5 days prior to Randomization/Baseline) or at the period of time prior to the start of the Initial Pain Assessment Period that is 5 times the half-life of the particular muscle relaxant used, whichever is greater.

- Pregabalin and gabapentin are prohibited beginning 48 hours prior to the start of the Initial Pain Assessment Period (the 5 days prior to Randomization/Baseline).

- Use of medical marijuana is prohibited beginning 48 hours prior to the start of the Initial Pain Assessment Period (the 5 days prior to Randomization/Baseline).

- All anti-depressants for the treatment of depression within 30 days prior to Screening (Appendix 4) with the exception of stable selective serotonin reuptake inhibitors (SSRIs). Anti-depressants prescribed for the treatment of chronic low back pain are prohibited 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 5 times the half-life of the particular anti-depressant, whichever is greater. Subjects who are anticipated to need to initiate treatment with an antidepressant during the Primary Efficacy Phase (Baseline to Week 16) should not be enrolled. Centrally acting agents such as sedative/hypnotics, anxiolytics, tranquilizers or benzodiazepines unless the subject's prescribed daily dose has remained unchanged throughout the previous 30 days and will remain unchanged throughout the study period (Appendix 4). Benzodiazepines prescribed as a muscle relaxant are prohibited and must be discontinued via washout. In this case, refer to Appendix 4, Muscle Relaxants.

- Herbal, homeopathic, and naturopathic remedies should not be initiated from the Initial Pain Assessment Period until Week 16; however, subjects who have taken a stable dose of these products for at least 30 days prior to the Initial Pain Assessment Period will be allowed to continue their regimen. Subjects should be advised that St. John's wort may interfere with the efficacy of hormonal contraceptive products.

- Botulinum toxin (Botox®) injection for chronic low back pain within 4 months prior to Screening.

5.8.1.4. Prohibited Non-pharmacological Therapies

- Commencing of physiotherapy is not allowed from the beginning of the Initial Pain Assessment Period through Week 16. This involves the requirement for new, concomitant physiotherapy including, but not limited to, transdermal electroneural stimulation (TENS), physical therapy, massage, acupuncture, and spinal manipulation. If the subject has had physiotherapy regularly for at least 4 weeks prior to Screening, the subject may participate in the study but should maintain this therapy at least through the Primary Efficacy Phase (up to Week 16). Facet joint injections and nerve blocks are prohibited beginning 30 days prior to IPAP and through Week 64.

5.8.2. Permitted Medications

Medications for other (non-chronic low back pain, non-pain) conditions are permitted provided the subject has received a stable dose for at least 30 days before the Initial Pain Assessment Period (30 days prior to Screening for antihypertensive medications) and the dose is not expected to change during the study. Note however, that dose adjustments (including starting a new therapy) during the study can be made if required, and recorded on the concomitant medication CRF. Subjects taking cytochrome (CYP3A4/5) enzyme inducers (eg, carbamazepine and rifampin) should be advised that these agents may interfere with the efficacy of hormonal contraceptive products.

- Occasional use of pain medications for pain is permitted in situations such as outpatient diagnostic procedures (eg, colonoscopy, dental procedures) or limited accidental injury (eg, ankle sprains, minor fractures, minor burns/sunburns). The subject should be counseled to avoid scheduling prospective procedures such that pain medications would be needed within 48 hours of a study visit. Contact the study monitor 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 5.8.1.2 above.

- Low-dose aspirin therapy for cardiac prophylaxis (≤325 mg per day or per local prescribing practice).

- After the Week 16 visit, subjects may initiate pregabalin, gabapentin, skeletal muscle relaxants, benzodiazepines, sedative/hypnotics, anxiolytics, anti-depressants (with the exception of monoamine oxidase inhibitors [MAO] inhibitors), and topical analgesics. Subjects should be counseled to consult with the study site before initiating any new therapy and Investigators should evaluate any new therapy for potential for adverse interactions with tramadol PR or rescue therapy by consulting the product labeling.

- At the discretion of the Investigator, standard of care treatments for chronic low back pain may be initiated for subjects who have completed the Week 64 visit or for subjects who have prematurely discontinued study medication provided 16 weeks have elapsed since the last dose of SC study medication. In this study, standard of care treatment refers to analgesics or other treatments approved by FDA (for US subjects) or another applicable Health Authority (for non-US subjects) and generally considered effective therapy for chronic low back pain. These medications include but are not limited to opioids, topical analgesics, NSAIDs, coxibs, tapentadol, tricyclic anti-depressants, benzodiazepines, or tramadol, and are prescribed at the discretion of the Investigator. Standard of care treatments are not considered study medication but the cost of pre-specified analgesics will be paid for by Pfizer, if allowed per local regulation while the subject is participating in the Follow-up Period. Their use will be recorded on the concomitant medication CRF.

5.9. Rescue Therapy

Subjects will be provided with rescue medication (acetaminophen/paracetamol caplets, tablets or capsules).

During the Washout Period and the Initial Pain Assessment Period (ie, prior to Baseline [Randomization]), subjects may take rescue medication as needed up to a maximum daily dose of 3000 mg per day. Rescue medication must be discontinued 24 hours prior to the Baseline (Randomization) visit.

In the event of inadequate pain relief for chronic low back pain during the double-blind Treatment Period, beginning at the Baseline (Randomization) visit through Week 16, subjects may take acetaminophen/paracetamol up to 3 days per week up to a maximum daily dose of 3000 mg per day. Subjects must discontinue rescue medication within 24 hours of any scheduled site visit prior to any scheduled study visit at which efficacy data is collected (ie, up to the Week 64 visit that occurs 16 weeks after the last dose of SC investigational product)..

From the Baseline (Randomization) visit through Week 16, subjects taking greater than 3 days per week of rescue medication (any level of acetaminophen/paracetamol used specifically for chronic low back 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 records. 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 pain relief for chronic low back pain should be withdrawn from study treatment and entered in the Early

Termination Follow-up Period (See Section 6.20.1). 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 remain in the study. However, if these subjects continue to take rescue medication more than 3 days per week, they should be withdrawn from study treatment.

After the Week 16 visit, subjects may take acetaminophen/paracetamol rescue medication daily, up to the maximum permitted dose of 3000 mg per day. After Week 64, subjects may be started on standard of care treatments for low back pain. After Week 64, subjects may continue to use acetaminophen/paracetamol as needed up to the maximum dose per day as permitted by local or national labeling.

Up to 16 weeks after the last dose of SC study medication, subjects who discontinue treatment and enter the Early Termination Follow-up Period may take acetaminophen/paracetamol rescue medication daily up to the maximum permitted dose of 3000 mg per day. After the second Early Termination Follow-up visit occurring approximately16 weeks after the last SC dose of study medication, subjects may be started on standard of care treatments for low back pain. After the second Early Termination Follow up visit, subjects may continue to use acetaminophen/paracetamol as needed up to the maximum dose per day as permitted by local or national labeling.

Subjects should return rescue medication bottles at each study visit for assessment of compliance.

Subjects will be instructed that many over-the-counter medications contain acetaminophen/paracetamol, and to guard against overuse. Subjects will be instructed to keep a daily record of their acetaminophen/paracetamol rescue medication usage via the IRT through Week 16. After Week 16 and through the Week 80 visit, usage of acetaminophen/paracetamol rescue medication will be recorded once weekly via the IRT. Subjects must discontinue rescue medication within 24 hours of any scheduled site visit prior to any scheduled study visit at which efficacy data is collected (ie, up to the Week 64 visit that occurs 16 weeks after the last dose of SC investigational product). Use of acetaminophen/paracetamol for other types of pain or illness during the study (eg, toothache, headache, fever) should be recorded as a concomitant medication on the appropriate CRF page.

6. STUDY PROCEDURES

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

The study visit windows are ±2 days for the dose titration visit at Week 2 and ±3 days for the visit at Week 4. The study visit windows are ±7 days for the clinic visits at Weeks 8, 16, 24, 32, 40, 48 and 56 and for the visits during the Follow-up Period and for the Early Termination Visits. The study visit windows are ±2 days for the telephone visits at Weeks 1 and 3, ±7 days for the telephone visits at Weeks 12, 20, 28, 36, 44, 52, 60, 68, 72,

76 and during the Early Termination Follow-up. In the event the subject requires a visit within the extremes of the visit windows, the following study visits should be scheduled with reference to the original baseline visit date as much as possible. Subject scheduling issues should be brought to the attention of the study monitor for resolution. Dosing visits should occur no earlier than 7 weeks from the previous injection. The Week 24 X-rays may be obtained up to 30 days before the Week 24 visit, but must be completed and read by the Central Reader before the Week 24 dose of SC study medication is administered. The visit window for the Week 56 X-rays is ±30 days from the nominal time point of the visit. The window for the Week 80 X-rays is ±30 days of the nominal time of the visit but should be obtained as close as possible to the Week 80 visit, and preferably no more than 14 days after the Week 80 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 allowed duration for Screening is 37 days, which includes the Washout Period and the 5 day Initial Pain Assessment Period.

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.

History of insufficient pain relief, inability to tolerate or contraindications to at least 3 different categories of commonly used agents for the treatment of chronic low back pain (Table 2) should 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 contraindication or if the subject refuses to take the medication due to fear of known side effects, this should also be clearly documented with supporting detail.

X-rays of the hips knees and shoulders and other major joints exhibiting signs or symptoms suggestive of osteoarthritis should be obtained and sent to the imaging Central Reader for assessment of joint-related eligibility. It is recommended that the radiographs required at Screening be obtained at least two weeks prior to the Baseline visit to permit central radiology review of the images and to establish subject eligibility for initial dosing in the study. Confirmation of radiologic eligibility from the Central Reader is required before the subject is randomized.

Clinically significant abnormal laboratory tests or tests not meeting inclusion/exclusion criteria may be repeated for verification prior to Baseline.

6.1.1. Activities at Screening

- Informed consent.
- History of insufficient pain relief, inability to tolerate, or contraindications to at least 3 different categories of commonly used agents for the treatment of chronic low back pain should be clearly documented on the appropriate CRF page.
- General medical history.
- Assessment of depression by medical history (Use of PHQ-9 is optional and suggested as a tool to assess seriousness of depression if needed. If the PHQ-9 is utilized, the completed questionnaire should be archived in the subject's source documents). (Appendix 5).
- Date of onset and primary etiology of primary diagnosis (chronic low back pain).
- Quebec Task Force in Spinal Disorders category. (Appendix 1).
- Comprehensive musculoskeletal/joint related medical history.
- Review of prior medication (record all protocol-qualifying medications for chronic low back pain, prior 12 month use of all other medications for chronic low back pain, prior 30 day use for all other medications).
- Demographics, Weight and Height with BMI calculation, Smoking Status, Alcohol Use/Dependency, Female Hormonal Status (if known or pending laboratory results).
- Sitting vital signs after sitting for at least 5 minutes, (blood pressure, and heart rate).
- Orthostatic blood pressure (supine/standing) measurement.
- General Physical Examination.
- Musculoskeletal physical examination.
- Neurologic exam/Neuropathy Impairment Score.
- ECG (12-lead).
- Survey of Autonomic Symptoms.
- LBPI score. At the screening visit only, in order to determine eligibility, the LBPI score will be collected at the study visit via the IRT.

- Clinical laboratory tests (blood chemistry, hematology, and urinalysis, serum Hepatitis B, C, and HIV screen, urine toxicology screen, HbA1c), serum pregnancy testing, FSH level to confirm post menopausal status for women who have not had a hysterectomy or bilateral oophorectomy, and who have been amenorrheic for at least 12 months but less than 24 months with no alternative pathological or physiological cause.

- X-rays of the hips, knees, and shoulders (and other major joints exhibiting signs or symptoms suggestive of osteoarthritis) will be obtained and sent to the imaging Central Reader for assessment of joint-related eligibility.

- Assessment of pain in the hips, knees, and shoulders and any major joint that will be imaged.

- Subject eligibility and inclusion/exclusion review (pending results of laboratory tests, ECG and central reading of X-rays). If a subject qualifies other than pending results he/she may begin the Washout Period. Sites will contact subjects who are found to be ineligible subsequent to the receipt of disqualifying laboratory, ECG or X-ray results to return requested study related materials and exit the Screening Period (Screen Failure).

- The Investigator or designee will confirm that female subjects of child bearing potential have selected 2 highly effective forms of contraception from the list of acceptable methods, and instruct the subject in their consistent and correct use. Document the conversation in the subject's chart.

- Dispense rescue medication; subjects will be instructed on the permissible amounts of rescue medication during the washout period, during the Initial Pain Assessment Period and during the treatment period, as well as the need to refrain from rescue medication use 24 hours prior to a study visit (Refer to Sections 6.2 and 6.3 below).

- Subjects will be instructed in the use of the IRT system to record daily LBPI scores, daily rescue medication use, weekly joint pain entries, weekly concomitant NSAID use entries with specific instructions as when to test the system and when to begin entering data.

6.2. Washout Period

Subjects who satisfy inclusion/exclusion criteria (to this point) will be provided with a washout schedule for current pain medications. The beginning of the Washout Period will preferably be scheduled based on the planned Baseline Visit so as to minimize the time spent without analgesic medications prior to Randomization. The Washout Period will include the discontinuation and washout of all pain medications, muscle relaxants, and anti-depressants for the treatment of low back pain for at least 5 half-lives prior to the Initial Pain Assessment Period and will be at a minimum 2 days or 48 hours (Refer to Appendix 4). Acetaminophen/paracetamol rescue medication will be dispensed. Subjects experiencing

pain during the Washout Period may take acetaminophen/paracetamol as needed up to a maximum daily dose of 3000 mg per day, but must discontinue rescue medication for at least 24 hours prior to the Baseline (Randomization) Visit.

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

6.3. Initial Pain Assessment Period

The Initial Pain Assessment Period will begin 5 days prior to the Randomization/Baseline Visit (Day 1). Subjects who do not require a washout of prohibited pain medications may begin the Initial Pain Assessment Period the day after X-ray confirmation of radiographic eligibility has been received from the Central Reader. During this time, the subject will record his/her daily LBPI scores, and rescue medication use via the IRT. In the event the subject misses an assessment entry in this period the schedule may be adjusted to acquire at least 4 days of daily LBPI score entries into the IRT (within a 5 day consecutive period prior to Baseline). Study sites will monitor the IRT reports for compliance with diary recordings and rescue medication use and reschedule those subjects who fail to provide at least 4 days of diary entries or fail to refrain from rescue medication use 24 hours prior to Baseline.

6.4. Baseline Visit (Day 1)

6.4.1. Assessment of Randomization Criteria and Randomization

Subjects must continue to satisfy Inclusion/Exclusion Criteria [general criteria and those specific to the Baseline (Day 1) visit – refer to Section 4.3] to be eligible for Randomization. Full eligibility should be assessed before carrying out randomization in the IRT system.

Subjects will undergo the following assessments prior to randomization:

- Review concomitant medication and confirm that the subject has complied with the washout period for analgesics.
- Review subject compliance with daily assessments of low back pain (LBPI score) and confirm that the subject has entered at least 4 LBPI scores on the daily pain diary in the 5 days prior to the Baseline (Day 1) visit, with an average LBPI score of ≥5.
- Review subject compliance with daily entry of rescue medication use and confirm that the subject has abstained from taking rescue medication (acetaminophen/paracetamol) within the 24 hours that precede dosing.
- Review subject compliance with joint pain assessments/ review joint pain scores.
- Administer Patient's Global Assessment of Low Back Pain (Appendix 7) and confirm that the score meets the inclusion requirements (Inclusion 8).
- Review the ECG and laboratory results and confirm that there are no clinically significant or exclusionary findings.

- Confirm that the Central Reader has reviewed the subject's baseline X-rays and confirmed radiographic eligibility of the subject.
- Confirm that females of childbearing potential are using two (2) methods of highly effective contraception and agree to continue two (2) methods of highly effective contraception for 112 days (16 weeks) after last dose of investigational product.
- Orthostatic blood pressure (supine/standing) measurement.
- Urine pregnancy test for females of childbearing potential (must be negative).

6.4.2. Pre-dosing (Day 1)

Subjects satisfying eligibility requirements will be randomized via an IRT system. The randomization number assigned to the subject will be provided by the system. Subjects satisfying eligibility requirements will undergo the following assessments prior to the first dose of study drug. Some of these may be performed prior to randomization for convenience.

- Brief Pain Inventory—short form (BPI-sf). (Appendix 8).
- RMDQ. (Appendix 6).
- WPAI:LBP. (Appendix 9).
- Health Care Resource Utilization.
- EQ-5D-5L. (Appendix 11).
- NIH pain consortium CLBP minimum dataset.
- Pain DETECT. (Appendix 12).
- Musculoskeletal Physical Examination.
- Neurologic exam/Neuropathy Impairment Score.
- Vital signs after sitting for at least 5 minutes, (blood pressure and heart rate).
- Clinical laboratory tests (blood chemistry, hematology, serum and plasma retention samples).
- Blood sample for Anti-Drug Antibody assessment (see Assessments; Anti-Drug Antibodies (Section 7.3.10).
- Blood samples for Pharmacokinetics (PK) and Pharmacodynamics (PD[NGF]) analyses (see Assessments; Pharmacokinetics and Pharmacodynamics Section 7.5).

- Blood samples for biomarkers (fasting if possible, status recorded on CRF) (see Section 7.6).
- Urine samples for biomarkers (Second void of day, or after; fasting if possible, status recorded on CRF) see Section 7.6).
- Blood sample for banked biospecimens (see Section 7.7.1 Markers of Drug Response and Additional Research, Section 7.7.2).
- Dispense rescue medication.
- Remind female subjects of child-bearing potential of contraceptive requirements.
- Dispense tramadol/matching placebo (2 week supply of 100 mg tablets) and instruct subject on dosing regimen. Subjects should take the first dose of oral study medication after all pre-dose baseline tests but before SC study medication administration.

6.4.3. Dosing (Day 1)

Subjects will receive a single SC injection of blinded study medication according to the treatment assigned by the IRT system (see Section 5.1).

The administration of study drug must be performed by medical staff (as per local regulations) and where facilities to handle allergic reactions are available (eg, diphenhydramine hydrochloride for injection, epinephrine 1:1000 for management of acute or severe reactions such as anaphylaxis). Should a subject experience symptoms typical of an allergic reaction (eg, shortness of breath, anaphylaxis, urticaria, angioedema), then study drug administration should be discontinued immediately and permanently. Subjects will receive appropriate treatment such as corticosteroids, antihistamine, or acetaminophen/paracetamol at the discretion of the Investigator. No other dosage modifications are allowed.

6.4.4. Post Dosing (Day 1)

Subjects will be observed in clinic for at least 1 hour after dosing. The following assessments will be completed at approximately 1-hour post-dose:

- Review and record Adverse Events.

Each subject should be reminded to seek medical care and/or contact the Investigator if the subject experiences symptoms of an acute or severe hypersensitivity reaction (eg, shortness of breath, anaphylaxis, urticaria, angioedema) after leaving the clinic.

6.5. Oral Dose titration - Weeks 1 to 4

During Weeks 1 through 4, the oral medication dose may be adjusted as needed to find the subject's optimal dose of oral study medication that balances pain relief and tolerability. Escalation or dose reduction will be accomplished by adjusting the number of tramadol PR 100 mg tablets or matching placebo tablets taken each day. During the titration period,

subjects will be provided with instructions on how to take the oral study the dose of oral study medication that they take during the titration period will be recorded. All subjects will begin at Baseline with 1 tablet of oral study medication per day and the dose may be adjusted at Weeks 1, 2, and 3 by 1 tablet increments. There will be an additional opportunity to adjust the dose at Week 4, when the fixed dose of tramadol PR is assigned. Dose adjustments may be carried out no more frequently than every 5 days. The maximum dose is 3 tablets per day (tramadol PR 300 mg per day). Determinations of whether to increase or decrease the dose of the oral study medication should be made by medical staff (per local regulations) and the rationale for dose changes should be documented in the subject's chart. The site should aim to schedule the dose adjustment assessments every 7 days; however, if necessary, the schedule may be adjusted within the window of ±2 days but should be separated by a minimum of 5 days.

The dosing frequency may not be adjusted. The tablets should be taken once a day. The tablets may not be broken.

6.5.1. Week 1 (Telephone Visit)

- Assess compliance with oral study medication.
- Evaluate pain relief and tolerability of the oral study medication. Increase oral medication dosage if tolerability is acceptable and pain relief is not adequate.
- Review subject compliance with daily assessments of low back pain (LBPI score), daily entry of rescue medication use, weekly entry of NSAID use (if applicable) and weekly assessments of joint pain and reminder of continued compliance.
- Review rescue medication compliance (subjects record use daily using the IRT).
- Review/Update concomitant medication and monitor for violations of NSAID use limits.
- Review weekly joint pain scores, if applicable.
- Remind female subjects of child-bearing potential of contraceptive requirements.
- Review Adverse events. If adverse events dictate that the subject should be seen, an unscheduled visit may be conducted and pertinent exams conducted (eg, physical exam, neurological exam, ECG, clinical laboratory testing) depending on the nature of the event and the Investigator's clinical judgment.

6.5.2. Week 2 (Clinic Visit)

- BPI-sf. (Appendix 8).
- RMDQ. (Appendix 6).
- Patient's Global Assessment of Low Back Pain. (Appendix 7).

- Evaluate pain relief and tolerability of the oral study medication. Increase the dose or decrease the dose based on tolerability or pain relief.
- 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.
- Adverse Event review.
- Review subject compliance with daily assessments of low back pain (LBPI score), daily entry of rescue medication use, weekly entry of NSAID use (if applicable) and weekly assessments of joint pain and reminder of continued compliance.
- Review rescue medication compliance (subjects record use daily using the IRT).
- Review/Update concomitant medication and monitor for violations of NSAID use limits.
- Review weekly joint pain scores, if applicable.
- Collect oral study medication and review compliance.
- Blood samples for PK and PD (NGF) analyses (see Assessments; Pharmacokinetics and Pharmacodynamics Section 7.5).
- Remind female subjects of child-bearing potential of contraceptive requirements.
- Dispense rescue medication.
- Dispense oral study medication (ie, tramadol PR 100 mg tablets or matching placebo).

6.5.3. Week 3 (Telephone Visit)

- Assess compliance with oral study medication.
- Evaluate pain relief and tolerability of the oral medication. Increase the dose (if applicable) or decrease the dose (if applicable) based on tolerability or pain relief.
- Review subject compliance with daily assessments of low back pain (LBPI score), daily entry of rescue medication use, weekly entry of NSAID use (if applicable) and weekly assessments of joint pain and reminder of continued compliance.

- Review rescue medication compliance (subjects record use daily using the IRT).
- Review concomitant medication and monitor for violations of NSAID use limits.
- Review weekly joint pain scores, if applicable.
- Remind female subjects of child-bearing potential of contraceptive requirements.
- Adverse events review. If adverse events dictate that the subject should be seen, an unscheduled visit may be conducted and pertinent exams conducted (eg, physical exam, neurological exam, ECG, clinical laboratory testing) depending on the nature of the event and the Investigator's clinical judgment.

6.6. Week 4

At Week 4, the dose of tramadol PR or matching placebo will be fixed at 100 mg, 200 mg or 300 mg per day through Week 56. Tramadol PR tablet strengths of 100 mg, 200 mg or 300 mg will be dispensed.

Subjects who have achieved a stable dose of tramadol PR or placebo during the period from Baseline to Week 4 will be assigned to the tablet strength that corresponds to their current daily dose of oral study drug. For subjects who have insufficient pain relief or difficulty with tolerability of the oral study drug, an additional adjustment in dose may be made at Week 4 when assigning the fixed dose of study drug. This should be done with caution, however, since the subject will be obliged to remain at the dose strength assigned at Week 4 throughout the remainder of the treatment period (through Week 56). No additional dose adjustments are allowed after Week 4.

Note: For subjects participating in Europe, following the completion of the Week 16 visit through the Week 56 visit, the dose of tramadol PR or oral placebo may be decreased to a minimum of 100 mg per day. Clinical indications for dose reduction include intolerance or decreased low back pain intensity. If the dose of tramadol PR or oral placebo is reduced, it may later be re-escalated for reasons of inadequate pain control to a maximum of the previous individually titrated dose (Refer to Section 5.5.2).

Dose increases or decreases following the completion of the Week 16 visit to the Week 56 visit will occur at scheduled or unscheduled clinic visits and will be accomplished by changing the dosage strength of the tablets that are dispensed to subjects.

- Evaluate pain relief and tolerability of the oral medication. Increase the dose (if applicable) or decrease the dose (if applicable) based on tolerability or pain relief.
- BPI-sf. (Appendix 8).
- RMDQ. (Appendix 6).
- Patient's Global Assessment of Low Back Pain. (Appendix 7).

- 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.
- Adverse Event review.
- Review of subject compliance with daily assessments of low back pain (LBPI score), daily entry of rescue medication use, weekly entry of NSAID use (if applicable) and weekly assessments of joint pain and reminder of continued compliance.
- Review rescue medication compliance (subjects record use daily using the IRT).
- Review/Update concomitant medication and monitor for violations of NSAID use limits.
- Review weekly joint pain scores, if applicable.
- Collect oral study medication and review compliance.
- Blood samples for PK and PD (NGF) in a subset of subjects.
- Remind female subjects of child-bearing potential of contraceptive requirements.
- Dispense rescue medication.
- Dispense oral study medication (ie, tramadol PR 100 mg, 200 mg or 300 mg tablets or matching placebo).

6.7. Week 8

6.7.1. Predosing (Week 8)

- BPI-sf. (Appendix 8).
- RMDQ. (Appendix 6).
- Patient's Global Assessment of Low Back Pain. (Appendix 7).
- EQ-5D-5L. (Appendix 11).
- 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.
- Adverse Event review.
- Review of subject compliance with daily assessments of low back pain (LBPI score), daily entry of rescue medication use, weekly entry of NSAID use (if applicable) and weekly assessments of joint pain and reminder of continued compliance.
- Review rescue medication compliance (subjects record use daily using the IRT).
- Review/Update concomitant medication and monitor for violations of NSAID use limits.
- Review weekly joint pain scores, if applicable.
- Collect oral study medication and review compliance.
- Urine pregnancy test for childbearing females (must be negative).
- Blood samples for PK and PD (NGF) analyses (see Assessments; Pharmacokinetics and Pharmacodynamics Section 7.5).
- Blood sample for Anti-Drug Antibody assessment (see Assessments; Anti-Drug Antibodies Section 7.3.10).
- Remind female subjects of child-bearing potential of contraceptive requirements.
- Dispense rescue medication.
- Dispense oral study medication (ie, tramadol PR 100 mg, 200 mg or 300 mg tablets or matching placebo).

6.7.2. Dosing (Week 8)

Subjects will receive a single SC injection of blinded study medication according to the treatment assigned by the IRT system (see Section 5.1).

6.7.3. Post Dosing (Week 8)

Subjects will be observed in clinic for at least 1 hour after dosing. The following assessments will be completed at approximately 1-hour post-dose:

- Review and record Adverse Events.

Each subject should be reminded to seek medical care and/or contact the Investigator if the subject experiences symptoms of an acute or severe hypersensitivity reaction (eg, shortness of breath, anaphylaxis, urticaria, angioedema) after leaving the clinic.

6.8. Week 12 Telephone Visit

- Adverse Events review.
- Review of subject compliance with daily assessments of low back pain (LBPI score), daily entry of rescue medication use, weekly entry of NSAID use (if applicable) and weekly assessments of joint pain and reminder of continued compliance.
- Review rescue medication compliance (subjects record use daily using the IRT).
- Review/Update of concomitant medication and monitor for violations of NSAID use limits.
- Review weekly joint pain scores, if applicable.
- Assess compliance with oral study medication.
- Remind female subjects of child-bearing potential of contraceptive requirements.
- If adverse events dictate that the subject should be seen, an unscheduled visit may be conducted and pertinent exams conducted (eg, physical exam, neurological exam, ECG, clinical laboratory testing) depending on the nature of the event and the Investigator's clinical judgment.

6.9. Week 16 Primary – Primary Efficacy Timepoint

6.9.1. Predosing (Week 16)

Treatment response will be calculated by the IRT. Subjects must have ≥30% reduction in average LBPI score relative to Baseline and ≥15% reduction in average LBPI score relative to Baseline at any week from Week 1 to Week 15, in order to continue study treatment. Subjects who do not meet this response criterion will be discontinued from the Treatment Phase and will enter the 24 week Early Termination Follow-up (See Section 6.20).

- BPI-sf. (Appendix 8).
- RMDQ. (Appendix 6).
- Patient's Global Assessment of Low Back Pain. (Appendix 7).
- WPAI:LBP. (Appendix 9).
- EQ-5D-5L. (Appendix 11).
- NIH pain consortium CLBP minimum dataset.
- TSQM. (Appendix 16.
- mPRTI. (Appendix 15).

- 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
- Musculoskeletal Physical Examination.
- Adverse Event review.
- Review of subject compliance with assessments of LBPI score and joint pain. Instruct subjects that after the Week 16 visit the LBPI score, joint pain, rescue medication and NSAID use will be assessed once weekly using IRT (See Section 7.1.2).
- Review rescue medication compliance (subjects record use daily using the IRT).
- Review/Update concomitant medication and monitor for violations of NSAID use limits.
- Review weekly joint pain scores, if applicable.
- Collect oral study medication and review compliance.
- Urine pregnancy test for childbearing females (must be negative).
- Clinical laboratory tests (blood chemistry, hematology, serum and plasma retention samples).
- Blood samples for PK analyses (see Assessments; Pharmacokinetics and Pharmacodynamics Section 7.5).
- Blood sample for Anti-Drug Antibody assessment (see Assessments; Anti-Drug Antibodies Section 7.3.10).
- Remind female subjects of child-bearing potential of contraceptive requirements.
- Dispense rescue medication.
- Dispense oral study medication (ie, tramadol PR 100 mg, 200 mg or 300 mg tablets or matching placebo). *Note: For subjects participating in Europe, following the completion of the Week 16 visit through the Week 56 visit, the dose of tramadol PR or oral placebo may be decreased to a minimum of 100 mg per day, if clinically indicated. If the dose of tramadol PR or oral placebo is reduced, it may later be re-escalated for reasons of inadequate pain control to a maximum of the previous individually titrated dose (refer to Section 5.5.2).*

- Schedule the Week 24 X-rays of the hips, knees, and shoulders and any other joint imaged at Baseline. These X-rays maybe obtained up to 30 days before the Wee 24 study visit.

6.9.2. Dosing (Week 16)

Subjects will receive a single SC injection of blinded study medication according to the treatment assigned by the IRT system (see Section 5.1).

6.9.3. Post Dosing (Week 16)

Subjects will be observed in clinic for at least 1 hour after dosing. The following assessments will be completed at 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.

6.10. Week 20 Telephone Visit

- Adverse Events review.
- Review of subject compliance with weekly IRT assessments (LBPI score, joint pain, rescue medication use and NSAID use).
- Review weekly joint pain scores, if applicable.
- Review/Update of concomitant medication and monitor for violations of NSAID use limits.
- Review rescue medication compliance (subjects record use weekly using the IRT).
- Assess compliance with oral study medication.
- Remind female subjects of child-bearing potential of contraceptive requirements.
- If adverse events dictate that the subject should be seen, an unscheduled visit may be conducted and pertinent exams conducted (eg, physical exam, neurological exam, ECG, clinical laboratory testing) depending on the nature of the event and the Investigator's clinical judgment.
- Verify that follow up radiographs required for the Week 24 visit have been scheduled and will be completed (refer to Section 7.3.8).

6.11. Week 24 - Dosing Visit

6.11.1. Predosing (Week 24)

- Radiographic assessment (X-rays) of hips, knees, and shoulders, and any other major joint imaged at Screening or at-risk joint identified during the study period. Confirmation of continued radiographic eligibility from the Central Reader is required prior to Week 24 SC dosing. The X-rays may be obtained up to 30 days before the Week 24 visit in order to allow time to receive confirmation of continued radiographic eligibility from the Central Reader.
- BPI-sf. (Appendix 8).
- RMDQ. (Appendix 6).
- Patient's Global Assessment of Low Back Pain. (Appendix 7).
- EQ-5D-5L. (Appendix 11).
- Survey of Autonomic Symptoms. (Appendix 14).
- 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.
- Adverse Event review.
- Review of subject compliance with weekly IRT assessments (LBPI score, joint pain, rescue medication use and NSAID use).
- Review rescue medication compliance (subjects record use weekly using the IRT).
- Review weekly joint pain scores, if applicable.
- Review/Update concomitant medication and monitor for violations of NSAID use limits.
- Collect oral study medication and review compliance.
- Urine pregnancy test for childbearing females (must be negative).
- Remind female subjects of child-bearing potential of contraceptive requirements.
- Dispense rescue medication.

- Dispense oral study medication (ie, tramadol PR 100 mg, 200 mg, or 300 mg tablets or matching placebo).

6.11.2. Dosing (Week 24)

Subjects will receive a single SC injection of blinded study medication according to the treatment assigned by the IRT system (see Section 5.1).

6.11.3. Post Dosing (Week 24)

Subjects will be observed in clinic for at least 1 hour after dosing. The following assessments will be completed at approximately 1-hour post-dose:

- Review and record Adverse Events.

Each subject should be reminded to seek medical care and/or contact the Investigator if the subject experiences symptoms of an acute or severe hypersensitivity reaction (eg, shortness of breath, anaphylaxis, urticaria, angioedema) after leaving the clinic.

6.12. Weeks 28, 36, and 44 Telephone Visit

- Adverse Events review.
- Review of subject compliance with weekly IRT assessments (LBPI score, joint pain, rescue medication use and NSAID use).
- Review weekly joint pain scores, if applicable.
- Review/Update of concomitant medication and monitor for violations of NSAID use limits.
- Review rescue medication compliance (subjects record use weekly using the IRT).
- Assess compliance with oral study medication.
- Remind female subjects of child-bearing potential of contraceptive requirements.
- If adverse events dictate that the subject should be seen, an unscheduled visit may be conducted and pertinent exams conducted (eg, physical exam, neurological exam, ECG, clinical laboratory testing) depending on the nature of the event and the Investigator's clinical judgment.

6.13. Weeks 32, 40 and 48 Dosing Visits

6.13.1. Predosing (Weeks 32, 40 and 48)

At Week 32, treatment response will be calculated by the IRT. At the Week 32 visit subjects must have ≥30% reduction in average LBPI score relative to Baseline in order to continue study treatment. Subjects who do not meet this response criterion will be discontinued from the Treatment Phase and will enter the 24-week Early Termination Follow-up (See Section 6.20).

- BPI-sf. (Appendix 8).
- RMDQ. (Appendix 6).
- Patient's Global Assessment of Low Back Pain. (Appendix 7).
- **Week 40 only**: EQ-5D-5L. (Appendix 11)
- 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.
- Adverse Event review.
- Review of subject compliance with weekly IRT assessments (LBPI score, joint pain, rescue medication use and NSAID use).
- Review rescue medication compliance (subjects record use weekly using the IRT).
- Review weekly joint pain scores, if applicable.
- Review/Update concomitant medication and monitor for violations of NSAID use limits.
- Collect oral study medication and review compliance.
- Urine pregnancy test for childbearing females (must be negative).
- **Week 32 and Week 48 only**: Blood samples for PK analyses (see Assessments; Pharmacokinetics and Pharmacodynamics Section 7.5).
- **Week 32 and Week 48 only** Blood sample for Anti-Drug Antibody assessment (see Assessments; Anti-Drug Antibodies Section 7.3.10).
- **Week 48 only**: Blood samples for PD (NGF) analyses (see Assessments; Pharmacokinetics and Pharmacodynamics Section 7.5).
- Remind female subjects of child-bearing potential of contraceptive requirements.
- Dispense rescue medication.
- Dispense oral study medication (ie, tramadol PR 100 mg, 200 mg or 300 mg tablets or matching placebo).

6.13.2. Dosing (Weeks 32, 40 and 48)

Subjects will receive a single SC injection of blinded study medication according to the treatment assigned by the IRT system (see Section 5.1).

6.13.3. Post Dosing (Weeks 32, 40 and 48)

Subjects will be observed in clinic for at least 1 hour after dosing. The following assessments will be completed at approximately 1-hour post-dose:

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.

6.14. Week 52 Telephone Visit

- Adverse Events review.
- Review of subject compliance with weekly IRT assessments (LBPI score, joint pain, rescue medication use and NSAID use).
- Review weekly joint pain scores, if applicable.
- Review/Update of concomitant medication and monitor for violations of NSAID use limits.
- Review rescue medication compliance (subjects record use weekly using the IRT).
- Assess compliance with oral study medication.
- Remind female subjects of child-bearing potential of contraceptive requirements.
- If adverse events dictate that the subject should be seen, an unscheduled visit may be conducted and pertinent exams conducted (eg, physical exam, neurological exam, ECG, clinical laboratory testing) depending on the nature of the event and the Investigator's clinical judgment.
- Verify that follow up radiographs required for the Week 56 visit have been scheduled and will be completed (refer to Section 7.3.8).

6.15. Week 56 Visit - End of Treatment Visit

- Radiographic assessment (X-rays) of hips, knees, and shoulders, and any other major joint imaged at Screening or at-risk joint identified during the study period. The X-rays may be obtained within ±30 days of the Week 56 visit. Radiographs must be sent to the Central Reader for assessment.

- BPI-sf. (Appendix 8).
- RMDQ. (Appendix 6).
- Patient's Global Assessment of Low Back Pain. (Appendix 7).
- WPAI:LBP. (Appendix 9).
- EQ-5D-5L. (Appendix 11).
- NIH pain consortium CLBP minimum dataset.
- TSQM. (Appendix 16).
- mPRTI. (Appendix 15).
- Survey of Autonomic Symptoms. (Appendix 14).
- Vital signs after sitting for at least 5 minutes, (blood pressure and heart rate).
- Orthostatic blood pressure (supine/standing) measurement.
- ECG (12-lead).
- Body weight.
- General Physical Examination.
- Musculoskeletal Physical Examination.
- Neurologic exam/Neuropathy Impairment Score.
- Adverse Event review.
- Review of subject compliance with weekly IRT assessments (LBPI score, joint pain, rescue medication use and NSAID use).
- Review rescue medication compliance (subjects record use weekly using the IRT).
- Review weekly joint pain scores, if applicable.
- Review/Update concomitant medication and monitor for violations of NSAID use limits.
- Collect oral study medication and review compliance.
- Blood for serum pregnancy test for childbearing females.

- Blood samples for serum and plasma retention samples.
- Blood samples for PK and PD (NGF) analyses (see Assessments; Pharmacokinetics and Pharmacodynamics Section 7.5).
- Blood sample for Anti-Drug Antibody assessment (see Assessments; Anti-Drug Antibodies Section 7.3.10).
- Remind female subjects of child-bearing potential of contraceptive requirements.
- Dispense rescue medication.

At Week 56, subjects will enter the Follow-up Period which lasts until Week 80.

6.16. Week 60– Telephone Visit

- Adverse Events review.
- Review of subject compliance with weekly IRT assessments (LBPI score, joint pain, rescue medication use and NSAID use).
- Review weekly joint pain scores, if applicable.
- Review rescue medication compliance.
- Review/Update of concomitant medication and monitor for violations of NSAID use limits.
- Remind female subjects of child-bearing potential of contraceptive requirements.
- If adverse events dictate that the subject should be seen, an unscheduled visit may be conducted and pertinent exams conducted (eg, physical exam, neurological exam, ECG, clinical laboratory testing) depending on the nature of the event and the Investigator's clinical judgment.

6.17. Week 64 Visit- Safety Follow-Up Period

- BPI-sf. (Appendix 8).
- RMDQ. (Appendix 6).
- Patient's Global Assessment of Low Back Pain. (Appendix 7).
- WPAI:LBP. (Appendix 9).
- Health Care Resource Utilization.
- EQ-5D-5L. (Appendix 11).

- 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.
- Adverse Event review.
- Review of subject compliance with weekly assessments of joint pain, NSAID use, and rescue medication use and reminder of continued compliance (after Week 64 subjects no longer complete weekly assessments of low back pain, but continue to record rescue medication use and NSAID use).
- Review weekly joint pain scores, if applicable.
- Review rescue medication compliance (subjects record use weekly using the IRT).
- Review/Update concomitant medication and monitor for violations of NSAID use limits.
- Clinical laboratory tests (blood chemistry, hematology, serum and plasma retention samples).
- Blood for serum pregnancy test for childbearing females.
- Blood samples for PK and PD (NGF) analyses (see Assessments; Pharmacokinetics and Pharmacodynamics Section 7.5).
- Blood sample for Anti-Drug Antibody assessment (see Assessments; Anti-Drug Antibodies Section 7.3.10).
- Initiate standard of care medication for low back pain if determined appropriate by the Investigator.
- Remind female subjects of child bearing potential of contraceptive requirements if less than 16 weeks have elapsed since the last dose of SC study medication
- Dispense rescue medication.

6.18. Weeks 68, 72, and 76 – Telephone Visits

- Review/Update of concomitant medication.
- Review of subject compliance with weekly IRT assessments (joint pain, rescue medication use and NSAID use).

- Review weekly joint pain scores, if applicable.
- Adverse Events review.
- **Week 76**: Verify that follow up radiographs required for the Week 80 visit have been scheduled and will be completed (refer to Section 7.3.8).

6.19. Week 80 Visit-End of Study Visit

- Radiographic assessment (X-rays) of hips, knees, and shoulders, and any other major joint imaged at Screening or at-risk joint identified during the study period. The window for the Week 80 X-rays is ±30 days of the nominal time of the visit but should be obtained as close as possible to the Week 80 visit, and preferably no more than 14 days after the Week 80 visit.
- RMDQ. (Appendix 6).
- Health Care Resource Utilization.
- Survey of Autonomic Symptoms. (Appendix 14).
- Vital signs after sitting for at least 5 minutes, (blood pressure and heart rate).
- Orthostatic blood pressure (supine/standing) measurement.
- ECG (12-lead).
- Musculoskeletal Physical Examination.
- Neurologic exam/Neuropathy Impairment Score.
- Adverse Event review.
- Review weekly joint pain scores, if applicable, weekly NSAID use entries and weekly rescue medication use.
- Review/Update concomitant medication.
- Blood sample for Anti-Drug Antibody assessment (see Assessments; Anti-Drug Antibodies Section 7.3.10).

6.20. Subject Withdrawal/Early Termination Visits

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

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. 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 the subject's outcome, if possible. The Investigator should inquire about the reason for withdrawal, request the return of all unused investigational product, 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 SC study medication.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. Pfizer may retain and continue to use any data collected before such withdrawal of consent.

Subjects who discontinue from treatment prior to Week 56, whether 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, as described in 6.20.1. In addition, subjects will be asked about the presence and severity of joint pain (hips, knees, and shoulders), rescue medication use, and NSAID use once per week via IRT through the end of the 24-week follow-up period.

X-rays of the hips, knees and shoulders (and any other major 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 study medication (as described in 6.20.1.1).

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 SC study medication to collect safety and efficacy data. Once the clinic visit 16-weeks after the last administration of SC study medication has been completed and final efficacy assessments have been collected, standard of care treatment may 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 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 SC study medication. That visit, (described in 6.20.1.5), includes repeat X-rays of the hips, knees and shoulders 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 before or 14 days after the nominal time of the visit. Telephone contact will be made with subjects at approximately 12 and 20 weeks following the last SC dose of study treatment. Every effort should be made to have the subject agree to complete the entire 24 week Early Termination Safety Follow-Up described above.

In the event that a subject refuses the Early Termination Safety Follow-up or chooses to discontinue during the Safety Follow-up Period (after Week 56 of the study through Week 80), a complete early termination visit should be performed. This early termination visit should include all procedures scheduled for the Week 64 and Week 80 visits, unless Week 64 has already been completed; in that case, only Week 80 procedures will be required. In addition, if the Week 56 visit was not completed prior to termination, body weight, a general physical examination, TSQM mPRTI, and NIH Pain Consortium CLBP minimum dataset 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 SC study medication.

Subjects entered in the Early Termination Follow-up Period will be able to take acetaminophen/paracetamol rescue medication daily up to the Early Termination Visit 2 that occurs 16 weeks after the last dose of study medication, but will be advised not to exceed the maximum daily dose of 3000 mg. Subjects will be requested not to take acetaminophen/paracetamol (or any other analgesic) in the 24 hours that precede in-clinic visits at which efficacy assessments are collected (Up to and including Week 64 and Early Termination Follow-Up period Visits 1 and 2, which occur 8 and 16 weeks after the last dose of SC study medication, respectively). After the second Early Termination Follow-up visit occurring approximately 16 weeks after the last SC dose of study medication, subjects may be started on standard of care treatments for low back pain. Subjects may continue to use acetaminophen/paracetamol as needed up to the maximum dose permitted by local or national labeling.

6.20.1. Early Termination Follow-Up Procedures

6.20.1.1. Early Termination Follow-Up Period Visit 1 (8 Weeks after the Last Dose of SC Study Medication)

- X-rays of the hips, knees and shoulders and all joints for which X-rays were obtained at Screening and other at risk joints identified during the study period, provided 30 days have elapsed since the last set of study X-rays were collected. These X-rays should be collected as soon as possible after the decision to withdraw was made, provided that 30 days have elapsed since the last set of study X-rays were collected.
- BPI-sf. (Appendix 8).
- RMDQ. (Appendix 6).
- Patient's Global Assessment of Low Back Pain. (Appendix 7).
- WPAI: LBP. (Appendix 9).
- EQ-5D-5L. (Appendix 11)
- NIH pain consortium CLBP minimum dataset.
- TSQM. (Appendix 16).

- mPRTI. (Appendix 15).
- Survey of Autonomic Symptoms.
- Vital signs after sitting for at least 5 minutes, (blood pressure and heart rate).
- Orthostatic blood pressure (supine/standing) measurement.
- ECG (12-lead).
- Body weight.
- General Physical Examination.
- Musculoskeletal Physical Examination.
- Neurologic exam/Neuropathy Impairment Score.
- Adverse Event review.
- Review of subject compliance with weekly IRT assessments (LBPI score, joint pain, rescue medication use and NSAID use).
- Review weekly joint pain scores, if applicable.
- Review rescue medication compliance (subjects record use weekly using the IRT).
- Concomitant medication review/update and monitor for violations of NSAID use limits.
- Blood sample for serum pregnancy test for childbearing females.
- Blood samples for serum and plasma retention samples.
- Blood samples for PK and PD (NGF) analyses (see Assessments; Pharmacokinetics and Pharmacodynamics Section 7.5).
- Blood sample for Anti-Drug Antibody assessment (see Assessments; Anti-Drug Antibodies Section 7.3.10).
- Remind female subjects of child-bearing potential of contraceptive requirements.
- Dispense rescue medication.

6.20.1.2. Early Termination Follow-Up Period-Telephone Visit (12 Weeks Post Last SC Dose)

- Adverse Events review.
- Review of subject compliance with weekly IRT assessments (LBPI score, joint pain, rescue medication use and NSAID use).
- Review weekly joint pain scores, if applicable.

- Review/Update of concomitant medication and monitor for violations of NSAID use limits.
- Collection of rescue medication use and compliance review.
- Remind female subjects of child-bearing potential of contraceptive requirements.

6.20.1.3. Early Termination Follow-Up Period Visit 2 (16 Weeks after Last Dose of SC Study Medication)

- BPI-sf. (Appendix 8).
- RMDQ. (Appendix 6).
- Patient's Global Assessment of Low Back Pain. (Appendix 7).
- WPAI:LBP. (Appendix 9).
- EQ-5D-5L. (Appendix 11).
- HCRU.
- Musculoskeletal Physical Examination.
- Neurologic exam/Neuropathy Impairment Score.
- Vital signs after sitting for at least 5 minutes, (blood pressure and heart rate).
- Orthostatic blood pressure (supine/standing) measurement.
- Adverse Event review.
- Review of subject compliance with weekly assessments of joint pain and reminder of continued compliance (after Early Termination Visit 2, subjects no longer complete weekly assessments of low back pain, but continue to record rescue medication, NSAID use, and joint pain).
- Review weekly joint pain scores, if applicable.
- Review rescue medication compliance (subjects record use weekly using the IRT).
- Concomitant medication review/update and monitor for violations of NSAID use limits.
- Clinical laboratory tests (blood chemistry, hematology, serum and plasma retention samples).

- Blood sample for serum pregnancy test for childbearing females.
- Blood sample for Anti-Drug Antibody assessment (see Assessments; Anti-Drug Antibodies Section 7.3.10).
- Blood samples for PK and PD (NGF) analyses (see Assessments; Pharmacokinetics and Pharmacodynamics Section 7.5).
- Initiate standard of care medication for low back pain if determined appropriate by the Investigator.

6.20.1.4. Early Termination Follow-Up Period Telephone Visit (20 Weeks Post Last Dose)

- Review/Update of concomitant medication.
- Review subject compliance with weekly IRT entries.
- Review weekly joint pain scores, if applicable.
- Adverse Events review.

6.20.1.5. Early Termination Follow-Up Period Visit 3 (24 Weeks after Last Dose)

- Radiographic assessment (X-rays) of hips, knees, and shoulders and any other major joint for which a radiograph was obtained at the Screening visit, and any other at risk joint identified as at risk during the study period. The window for the Early Termination Visit 3 X-rays is ±30 days of the visit, but the X-rays should be obtained as close as possible to the Early Termination Visit 3, but not more than 30 days before or preferably 14 days after the visit.
- RMDQ. (Appendix 6).
- Health Care Resource Utilization.
- Survey of Autonomic Symptoms (SAS). (Appendix 14)
- Vital signs after sitting for at least 5 minutes, (blood pressure and heart rate).
- Orthostatic blood pressure (supine/standing) measurement.
- ECG (12-lead).
- Musculoskeletal Physical Examination.
- Neurologic exam/Neuropathy Impairment.
- Review weekly joint pain scores, if applicable, weekly NSAID use entries and weekly rescue medication use.
- Review/Update of concomitant medication.

- Blood sample for Anti-Drug Antibody assessment (see Assessments; Anti-Drug Antibodies Section 7.3.10).
- Adverse Events review.

6.20.2. Procedures for Subjects Undergoing Joint Replacement

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

Subjects who undergo total knee, hip or shoulder joint replacement surgery during the study (Treatment Period or Follow-up Period) will be followed for 24 weeks after the procedure (See Appendix 18), as part of the substudy or in a separate protocol, provided the subject consents. The follow up will be conducted as part of a substudy if the total joint replacement occurs before the last subject enrolled in Study A4091059 has completed the treatment period. Subjects undergoing total joint replacements after the last subject completes the treatment period may be followed in a separate protocol (Study A4091064).

Transition procedures into the substudy or Study A4091064 are determined by the timing of total joint replacement surgery:

- Subjects who have undergone or plan an immediate total joint replacement procedure will be discontinued from the treatment period and enter into the substudy or Study A4091064. At the discontinuation visit, all End of Treatment (Week 56) and Week 64 procedures should be completed (Sections 6.15 and 6.17); unless the Subject has already completed the Week 56 and Week 64 visits, in which case only the Week 80 visit procedures should be completed (Section 6.19). Baseline visit activities (See Appendix 18, Schedule of Activities) should be completed on the same days as the End of Treatment Visit. 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 study medication.

- Subjects who plan to undergo total joint replacement during the study will be discontinued from the treatment period and entered into Early Termination Follow-up (See Section 6.20) until their joint replacement or other arthroplasty procedure. For these subjects, a complete early termination visit (which includes all Week 56 and Week 64 activities) should be conducted prior to the total joint replacement or arthroplasty procedure (Section 6.20) and entrance into the substudy or Study A4091064. Substudy or Study A4091064 Baseline visit activities (See Appendix 18, Schedule of Activities) should be completed on the same day as the early termination visit. Subjects who have not undergone or scheduled total joint replacement surgery within the study treatment or safety follow-up period of this study will not be eligible for the total joint replacement substudy or Study A4091064.

Subjects who undergo other types of joint replacement surgery or arthroplasty during the study should be discontinued from study treatment and complete the protocol specified Safety Follow-up Period but not be entered into the substudy or Study A4091064 for follow-up.

7. ASSESSMENTS

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

7.1. Subject Collected Efficacy Assessments

7.1.1. Daily/Weekly Low Back Pain Intensity (LBPI) Score

Average back pain will be assessed with an 11-point Numeric Rating Scale ranging from zero (no pain) to 10 (worst possible pain) captured through an IRT daily from the beginning of the Initial Pain Assessment Period through to the Week 16 Visit. Beginning after the Week 16 visit through Week 64, the LBPI score will be captured weekly through an IRT.

The subjects should describe their average low back pain during the past 24 hours by choosing the appropriate number from 0 to 10. If possible, the subject should conduct the self-assessment in the evening prior to midnight (Refer to Appendix 10, Subject Daily Assessments).

Example Question:

Select the number that best describes your average low back pain in the past 24 hours:

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Possible Pain

If an IRT is used, additional instructional language may need to be added to the question such as “Using a scale from 0 to 10, with 0 meaning no pain and 10 meaning worst possible pain; please enter the number that best describes your average low back pain in the past 24 hours.”

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/paracetamol tablets/caplets/capsules will be captured. The subject should note the number of tablets/caplets/capsules of rescue medication taken during the last 24 hours.

Following the Week 16 visit up to and including the Week 80 visit and up to and including the Early Termination Visit 3 for subjects that have entered the Early Termination Follow-Up Period, the use of acetaminophen/paracetamol as rescue medication will be collected once weekly using IRT. The subject will record the number of days rescue medication was used and maximum number of tablets, capsules or caplets of rescue medication taken on any day in the past week.

7.2. Study Efficacy Assessments

7.2.1. Roland Morris Disability Questionnaire (RMDQ)

The RMDQ is an index of how well subjects with low back pain are able to function with regard to daily activities.[38] The score for the index ranges from 0 to 24 with a lower score indicating better function. All subjects will complete the RMDQ via IRTat the study center at Baseline, and Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, 64, and 80 (or Early Termination Visits 1, 2, and 3, see Section 6.20.1) visits. An example of the RMDQ can be found in Appendix 6.

7.2.2. Patient's Global Assessment of Low Back Pain

The Patient's Global Assessment of Low Back Pain (Appendix 7) is a global evaluation that utilizes a 5-point Likert scale with a score of 1 being the best (Very Good) and a score of 5 being the worst (Very Poor). It was adapted from a scale developed by Pfizer (Pharmacia) for studies in osteoarthritis (OA) and rheumatoid arthritis (RA). The original question asked in the OA/RA studies was modified to refer to low back pain rather than arthritis, otherwise the scale was unchanged. It is intended to provide a qualitative measurement of the subject's overall impression of disease activity. The Patient's Global Assessment of Low Back Pain will be completed by the subject via IRT at Baseline and the Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, and 64 (or Early Termination) visits. The subjects will answer the following question:

"Considering all the ways your low back pain 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

7.2.3. Brief Pain Inventory—short form (BPI-sf)

The BPI-sf was derived from the Brief Pain Inventory (BPI) developed for use in clinical research by Charles Cleeland. It is a self-administered questionnaire developed to assess the severity of pain and the impact of pain on daily functions during the 24-hour period prior to evaluation. It consists of 5 questions. Questions 1-4 measure the magnitude of pain at its worst, least, average, and 'right now'. Responses are provided by the subject on an 11-point

Numeric Rating Scale with anchors at 0 (No Pain) and 10 (Pain as bad as you can imagine). Question 5 consists of 7 item subsets (A to G) which measure the level of interference of pain on daily functions. Responses are given on an 11-point Numeric Rating Scale with anchors at 0 (Does not interfere) and 10 (Completely interferes). The instrument is scored by item and by dimension, with lower scores indicating less pain or pain interference. The BPI will be completed by the subject via IRT at Baseline and the Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, and 64 (or Early Termination Visits 1 and 2, see Section 6.20.1) visits. Refer to Appendix 8 for the BPI-sf questionnaire.

7.2.4. Work Productivity and Activity Impairment Questionnaire: Low Back Pain (WPAI:LBP)

Subjects will complete the WPAI:LBP (See Appendix 9) prior to SC dosing at Baseline, Week 16, 56, and 64 (or at Early Termination Visits 1 and 2, see Section 6.20.1). Subjects will record their responses using IRT.

The WPAI:LBP is a self-administered questionnaire that measures the effect of general health and symptom severity on work productivity and regular activities. Unlike general health or disease-specific measures, the WPAI:LBP assesses function-related endpoints to allow a measure of the economic impact of relative differences in either the safety or efficacy of therapeutic endpoints.[39] In this study, the WPAI:LBP will measure the effect of the subject's chronic low back pain on work productivity and regular activities.

7.2.5. Euro Quality of Life Health State Profile (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 a visual analog scale (VAS) item (see Appendix 11). The 5 item health state profile will be assessed to calculate a single index value. This instrument provides a mechanism for conducting cost-effectiveness and cost-utility analyses.[40] The 5-item Health State Profile and the visual analogue scale will be administered in this study at Baseline, Weeks 8, 16, 24, 40, 56 and 64 (or at Early Termination, Visits 1 and 2, see Section 6.20.1). Subjects will record their responses using IRT.

7.2.6. Treatment Satisfaction Questionnaire for Medication v.II (TSQM)

Subjects will complete the Treatment Satisfaction Questionnaire for Medication v.II (Appendix 16) via IRT at Weeks 16 and 56 (or at Early Termination Visit 1, as described in Section 6.20.1.1).

The TSQM is an 11-item validated scale that quantifies the subject's level of satisfaction with study medication, effectiveness and side effects/tolerability. Most items are scored on a 7-point Likert scale ranging from 'Extremely Satisfied' to 'Extremely Dissatisfied'. The domains of Effectiveness, Side Effects, Convenience and Global Satisfaction are scored from 0-100 with a higher score indicating greater satisfaction. The TSQM is self-administered by the subject and takes less than 5 minutes to complete.[42]

7.2.7. Patient Reported Treatment Impact Assessment-modified (mPRTI)

The mPRTI is a self-administered questionnaire containing four items to assess patient satisfaction, previous treatment, preference and willingness to continue using the study medication. In this study, three items are being collected: previous treatment, preference and willingness to continue using the study medication. Higher scores indicate greater preference or willingness to use the study medication; see Appendix 15. The questionnaire will be self-completed by the subject using IRT at Weeks 16 and 56 and at Early Termination Visit 1, as described in Section 6.20.1.1.

7.2.8. Health Care Resource Utilization

The utilization of health care resources (eg, doctor office visits, hospitalizations, surgeries or procedures, etc.) during the 3 month period prior to Baseline will be collected by a questionnaire via IRT. In addition, Health Care Resource Utilization will be collected at study visits at Week 64, and Week 80 (or at Early Termination, Visits 2 and 3, see Section 6.20.1).

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, 12 months for pain and other medications for the treatment and relief of symptoms of chronic low back pain [with the exception of protocol-qualifying medications for chronic low back pain, for which there is no limit on the recall time period]), 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 Week 56, or at Early Termination (as described in Section 6.20).

7.3.1.2. Musculoskeletal History and Physical Examination

Each subject will also undergo a musculoskeletal physical examination at Screening, Baseline, Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, 64 and 80 (or Early Termination as described in Section 6.20). 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, 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. Joint Pain Weekly Assessments

At the Screening visit, subjects will record via IRT if they are experiencing pain in the hips, knees, shoulders or any other major joint. Pain will be rated on an 11 point numeric rating scale, using a 24 hour recall. A major joint is defined as a mobile synovial joint in the limbs such as shoulders, elbows, wrists, hips, knees, ankle and excluding the joints of the toes and hands. The subject should record a score for any major joint that has signs and symptoms of osteoarthritis and thus will be undergoing X-ray.

On a weekly basis beginning at the Initial Pain Assessment Period and through Week 80 of the study (or through the last Early Termination Follow-up visit), the subject will be asked via the IRT if he/she experienced new onset or increased pain in any major joint. If a subject responds that he/she has experienced new onset or increased pain in a major joint (post-baseline), the subject will be asked to rate his/her pain in that joint on the same 11-point numeric rating scale, using a 24-hour recall and will be asked to rate his/her pain in that joint for the remainder of the study.

7.3.3. Collection of Concomitant NSAID Use

Use of over-the-counter or prescription NSAID use will be collected weekly via IRT from Baseline until the Week 80 visit. During the Early Termination Follow-Up Period, for subjects who discontinue treatment, the use of over-the-counter or prescription NSAID will be collected once weekly using IRT. Subjects will record the number of days of NSAID use in the past week. Via telephone contact or at clinic visits, sites will interview the subject regarding his/her NSAID use and record additional information, such as the medication name, dosage, and reason for use on a CRF. The investigator or designee should closely monitor the subject's NSAID use to detect subjects who are at risk of exceeding the protocol-defined limits on NSAID use (See Section 5.8.1.2).

7.3.4. Laboratory Safety Assessments

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

Chemistry	Hematology	Other	Urinalysis
Screening, Baseline, Weeks 16 and 64 (or Early Termination Visit 2): Sodium, potassium, chloride, bicarbonate, glucose (non fasting), Blood Urea Nitrogen (BUN), creatinine, calcium,	Screening, Baseline, Weeks 16 and 64 (or Early Termination Visit 2): Complete blood count with differential	Screening only: HbA1c Serum FSH, if applicable Hepatitis screen (eg, HBsAg, Anti-HCV), HIV test (HIV Ab screen) Urine toxicology screen	Screening only: pH, protein, glucose, ketones, blood, bilirubin, nitrite, specific gravity and leukocytes.

Chemistry	Hematology	Other	Urinalysis
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		(eg, for opiates, barbiturates, amphetamines, cocaine, propoxyphene, methadone, phencyclidine, and methaqualone). Screening, Weeks 56 64 (or Early Termination Visits 1 and 2): Serum Pregnancy Test Baseline, Weeks 8, 16, 24, 32, 40, and 48 (Pre-dose at dosing visits):Urine Pregnancy Test Baseline, Weeks 16, 56 and 64 (or Early Termination Visits 1 and 2): Serum and plasma retention samples	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).			

7.3.4.1. Blood Tests

Blood tests for clinical laboratory testing (chemistry, hematology) will be performed at Screening, Baseline, Week 16, and Week 64 (or at Early Termination Visit 2, as described in Section 6.20). An unscheduled visit(s) may be necessary for follow-up of abnormal test results.

Serum and plasma retention samples will be collected at Baseline, Weeks 16, 56, and 64 or at Early Termination Visits 1 and 2 (Refer to Section 6.20 for Early Termination procedures).

See Section 7.3.4.3 for sample collected for serum pregnancy test and 7.3.4.4 for sample collected for FSH testing.

Blood samples collected for PK, PD (NGF), biomarkers and anti-drug antibody measurements are described in Sections 7.5.1, 7.5.2, 7.6, and 7.3.10.

7.3.4.2. Urinalysis and Urine Toxicology Screen

Urinalysis will be performed at Screening only.

Urine toxicology screen will be performed at Screening only.

Urine samples collected for biomarker analyses are described in Section 7.6.2.

7.3.4.3. Pregnancy Tests

For female subjects of childbearing potential, a serum pregnancy test, with a sensitivity of at least 25 mIU/mL, will be performed during the Screening period. Urine pregnancy tests with sensitivity of at least 25 mIU/mL [redacted], will be performed at Baseline (Day 1, pre-dose), Weeks 8, 16, 24, 32, 40, and 48. A negative pregnancy result is required before the subject may receive the investigational product. Additional serum pregnancy tests will be conducted at Weeks 56 and 64 (to confirm the subject has not become pregnant during the study period) or at Early Termination Visits 1 and 2, as described in Section 6.20. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected), and may also be repeated as per request of Institutional Review Boards/Ethics Committees (IRB/ECs) or if required by local regulations. [redacted]

Refer to Sections 8.10 and 8.10.1 for guidance pertaining to exposure during pregnancy and post-natal follow-up.

7.3.4.4. Serum FSH Testing

Female subjects of non child bearing potential who have not had a hysterectomy or bilateral oophorectomy and who have been amenorrheic for at least 1 year with no alternative pathological or physiological cause must undergo serum FSH testing to determine post menopausal status. A serum FSH level within the laboratory's reference range for postmenopausal females is required. Female subjects who have been amenorrheic less than 1 year will be considered of child-bearing potential. Female subjects who are considered of childbearing potential do not require FSH testing.

7.3.5. Vital Signs

Vital signs (including systolic blood pressure, diastolic blood pressure, and pulse rate) will be collected and recorded at Screening, Baseline, prior to SC dosing at Weeks 2, 4, 8, 16, 24, 32, 40, 48, and at Weeks 56, 64 and 80 or at Early Termination (as described in Section 6.20). Vital signs will be collected after the subject has been in a sitting position for at least five minutes at each visit.

7.3.5.1. Orthostatic Blood Pressure Measurements

In addition to sitting vital sign measurements, orthostatic blood pressure measurements will be obtained using a standard manual sphygmomanometer at Screening, Baseline and at Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, 64 and 80 or at Early Termination (as described in Section 6.20). 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 mm Hg and 5 mm Hg, respectively, the supine blood pressure will be considered to be stable. The mean of the two stable replicate measures will be considered to represent the baseline supine blood pressure (mean systolic and mean diastolic blood pressure) for that visit. Once the supine blood pressure is considered to be stable, subjects will be asked to assume the standing position. After subjects have been in the standing position for 1 minute and 3 minutes, systolic and diastolic blood pressure will be measured and recorded for both timepoints. If the measurements do not meet the criteria for orthostatic (postural) hypotension, no further measurements are needed. If either the 1 minute 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.

Table 4. Orthostatic Blood Pressure Changes and Subject Management

Mean Supine Systolic Blood Pressure	Decrease in Blood Pressure Defining Orthostatic (postural) Hypotension	Actions (for both criteria)
≤150 mmHg	≥20 mmHg systolic **or** ≥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 and the following actions should be taken: Refer to Section 7.4.3 for guidance on determining which subjects with confirmed orthostatic hypotension will require consultation with a neurologist or cardiologist.
OR		
>150 mmHg	≥30 mmHg systolic **or** ≥15 mmHg diastolic	

7.3.6. 12-Lead Electrocardiogram

A 12-lead ECG will be performed at Screening, Weeks 16, 56 and 80 and at Early Termination Visits 1 and 3 (See Section 6.20.1) for determination of ECG-related eligibility and safety monitoring. Post Screening ECGs may be collected during the study, if needed (for cause), at the discretion of the investigator.

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, RR intervals and heart rate [HR]) will be collected. The QTc interval reading produced by machine will be listed in the data listings. The QT interval will be manually measured by the central laboratory. The cardiologist at the central ECG laboratory reading the ECGs will be blinded regarding study drug. In the event a clinically significant ECG abnormality is seen at a visit on a post treatment ECG, the investigator should consider evaluation of the subject by a cardiologist.

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

- Significant bradycardia (heart rate of ≤45 beats per minute on an ECG, exclusionary at Screening).
- Heart rate decrease from Screening of ≥25% with resulting heart rate <60 bpm.

Investigators should report adverse events of bradycardia for subjects who meet the ECG criteria listed above. Refer to Section 7.4.3 for additional details pertaining to subject evaluation and dosing in subjects with sympathetic function adverse events.

7.3.7. Survey of Autonomic Symptoms

The Survey of Autonomic Symptoms is a validated, easily administered instrument to measure autonomic symptoms that has been proposed to be valuable in assessing neuropathic autonomic symptoms in clinical trials (refer to Appendix 14).

Subjects will complete the Survey of Autonomic Symptoms at Screening, prior to SC dosing at Week 24, and at Weeks 56 and 80 (or at Early Termination Visits 1 and 3, as described in Section 6.20). Subjects will enter responses in IRT.

7.3.8. Radiographic Assessments

A central radiology reader (Central Reader) will review the radiology images for assessment of eligibility including determination and identification of exclusionary joint conditions such as rapidly progressive osteoarthritis, atrophic or hypotrophic osteoarthritis, subchondral insufficiency fractures, spontaneous osteonecrosis of the knee [SPONK], primary osteonecrosis, or pathological fractures.

During the study, the Central Reader will review radiology images for continued radiologic eligibility and for diagnosis of joint conditions that would warrant further evaluation by the Adjudication Committee such as rapidly progressive osteoarthritis, subchondral insufficiency fractures, spontaneous osteonecrosis of the knee (SPONK), primary osteonecrosis or pathological fracture.

Central radiologists (Central Readers) will be board certified radiologists or have the international equivalent as musculoskeletal radiologists. The Central Readers will be governed by an imaging atlas and an imaging Charter which includes a specific description of the scope of their responsibilities.

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

Radiographic assessments (X-rays) of the hips, knees and shoulders will be obtained at Screening, Weeks 24, 56 and 80 (or at Early Termination Visit 1 and 3, as described in Section 6.20). 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 shoulders, elbows, wrists, hips, knees, ankles and excluding the joints of the toes and hands. Any joint imaged at Screening or other at-risk joints identified during the study period should also be imaged at the same intervals as the knees, hips, and shoulders.

It is recommended that the radiographs required at Screening be obtained at least two weeks prior to the Baseline visit to permit central radiology review of the images and to establish subject eligibility for initial dosing in the study. Subjects will not be permitted to start dosing in the study until the Screening radiographs are reviewed by the Central Reader and eligibility is established. Radiographs required for the Week 24 visit may be conducted up to 30 days before the visit, but it is recommended that the Week 24 radiographs be obtained at least two weeks prior to the Week 24 visit to permit Central Reader review of the images and to establish eligibility for continuation in the study. Radiographs required for the Week 56 visit may be conducted within 30 days of the visit (ie, before or after the visit). The window for the Week 80 X-rays is ±30 days of the nominal time of the visit but should be obtained as close as possible to the Week 80 visit, and preferably no more than 14 days after the Week 80 visit.

The Central Reader will review the Week 24 knee X-rays to confirm continued radiologic eligibility and for evidence of radiographic progression of knee osteoarthritis. The Central Reader will identify subjects entering the study with asymptomatic knee osteoarthritis Kellgren Lawrence Grade 2 who progress to Kellgren Lawrence Grade ≥3 at Week 24. These subjects should be discontinued from tanezumab treatment and entered into the Early Termination Follow-up. The images from these patients will not be reviewed by the Adjudication Committee unless the Central Reader determines the subject has developed a joint condition that would require evaluation by the Adjudication Committee such as rapidly progressive osteoarthritis, subchondral insufficiency fractures, spontaneous osteonecrosis of the knee (SPONK), primary osteonecrosis or pathological fracture.

For subjects discontinue prior to the Week 56 visit, follow-up radiographs of the hips, knees and shoulders should be performed as soon as possible (refer to Section 6.20.1) after the decision to withdraw from the study has been made, provided at least 30 days have passed since the last set of X-rays were collected. A final set of follow-up radiographs of the hips, knees and shoulders should be obtained 24 weeks (Early Termination Visit 3,

Section 6.20.1.5) after the last dose of SC study treatment was administered. Any joint imaged at Screening or other at risk joints identified during the study period should also be imaged at Early Termination Visits 1 and 3.

For subjects who are identified by the Central Readers as having 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 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.

7.3.8.1. Radiation Exposure

The International Commission on Radiation Protection (ICRP) has developed and applied the ALARA principle in developing guidelines that balance the benefits of radiation exposures against possible risks. This principle states that human exposures to radiation should be "**A**s **L**ow **A**s **R**easonably **A**chievable, with economic and social considerations taken into account."

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

Radiograph	Annual Effective Dose (mSv)
Knee	0.024 mSV
Hip	1.9 mSV
Shoulder	0.04 mSV
Total	1.964 mSV

The average annual subject exposure per body part imaged is shown in the table above.[32,33] The annual total effective dose per subject in this study is expected to be approximately 2.0 mSv. This can be compared to the annual effective dose from natural background radiation of approximately 3.0 mSv. In some cases, it is expected that a repeat image of a joint may necessary due to the quality of the X-ray images.

7.3.9. Neurologic Examination

Neurologic examinations will be performed by the Investigator or designated physician and assessed for clinically significant changes from Baseline. The examinations will be performed at Screening, Baseline, and Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, 64 and 80 (or at Early Termination, as described in Section 6.20) and the Neuropathy Impairment Score (NIS) will be completed at these time points based on this neurological exam. 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 patients with neuropathy and which has been used to evaluate subjects for signs of peripheral neuropathy

in clinical trials.[24] Investigators and other designated physicians performing the neurologic examination 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.

A neurologic evaluation should be performed by a consulting neurologist if any of the following occurs:

- 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, pallanesthesia, paresthesia, peripheral sensory neuropathy, sciatica, sensory disturbance, sensory loss, tarsal tunnel syndrome) 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 study participation, 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.

In these cases, a neurologic evaluation should be obtained as soon as possible after these signs and symptoms are known. The results of the neurological consultation will be recorded on the appropriate CRF and adverse event (if applicable) forms. Adverse events will be reported where applicable as described in Section 8.

7.3.10. Anti-Drug Antibody Testing

Blood samples for the assessment of ADA against tanezumab (anti-tanezumab antibodies) will be collected at Baseline (Day 1; predose) and Weeks 8 (predose), 16 (predose), 32 (predose), 48 (predose), 56, 64 and 80. If subjects terminate prior to Week 56, ADA will be determined at approximately 8, 16 and 24 weeks after the last SC dose was administered (or at Early Termination, as described in Section 6.20).

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 will be provided to the Investigator site prior to initiation of the trial.

7.4. Triggered Requirements and Subject Level Stopping Rules

The following rules will apply to individual subjects at the time of the second and subsequent SC injections of study medication.

7.4.1. Dysesthesia/Allodynia

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

Unresolved dysesthesia/allodynia: Withhold the SC study medication for a maximum of 14 days beyond the planned dosing day to allow for resolution of the adverse event. If the dysesthesia/allodynia has not resolved within the 14 day period after the scheduled dosing date, the subject will not receive any additional doses of study medication and will enter the Early Termination Follow-up Period (see Section 6.20).

7.4.2. Hypersensitivity or Injection Site Reactions

If a severe hypersensitivity reaction or severe injection reaction occurs following the administration of SC study medication, study drug should be discontinued immediately and no further administrations of SC study medication will be allowed. Subjects experiencing these types of reactions will enter the Early Termination Follow-up Period (see Section 6.20).

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 7.3.5.1 will be designated as confirmed orthostatic hypotension episode and should be reported as an adverse event whether or not the subject had accompanying symptoms.

Confirmed episodes of orthostatic hypotension: If a confirmed episode of orthostatic hypotension occurs (as defined in Section 7.3.5.1) it should be reported as an adverse event and the subject should be further evaluated as described below to determine if a neurology or cardiology consultation should be obtained and/or whether further treatment with study medication should occur. Figure 2 provides a flow diagram for the processes described below.

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

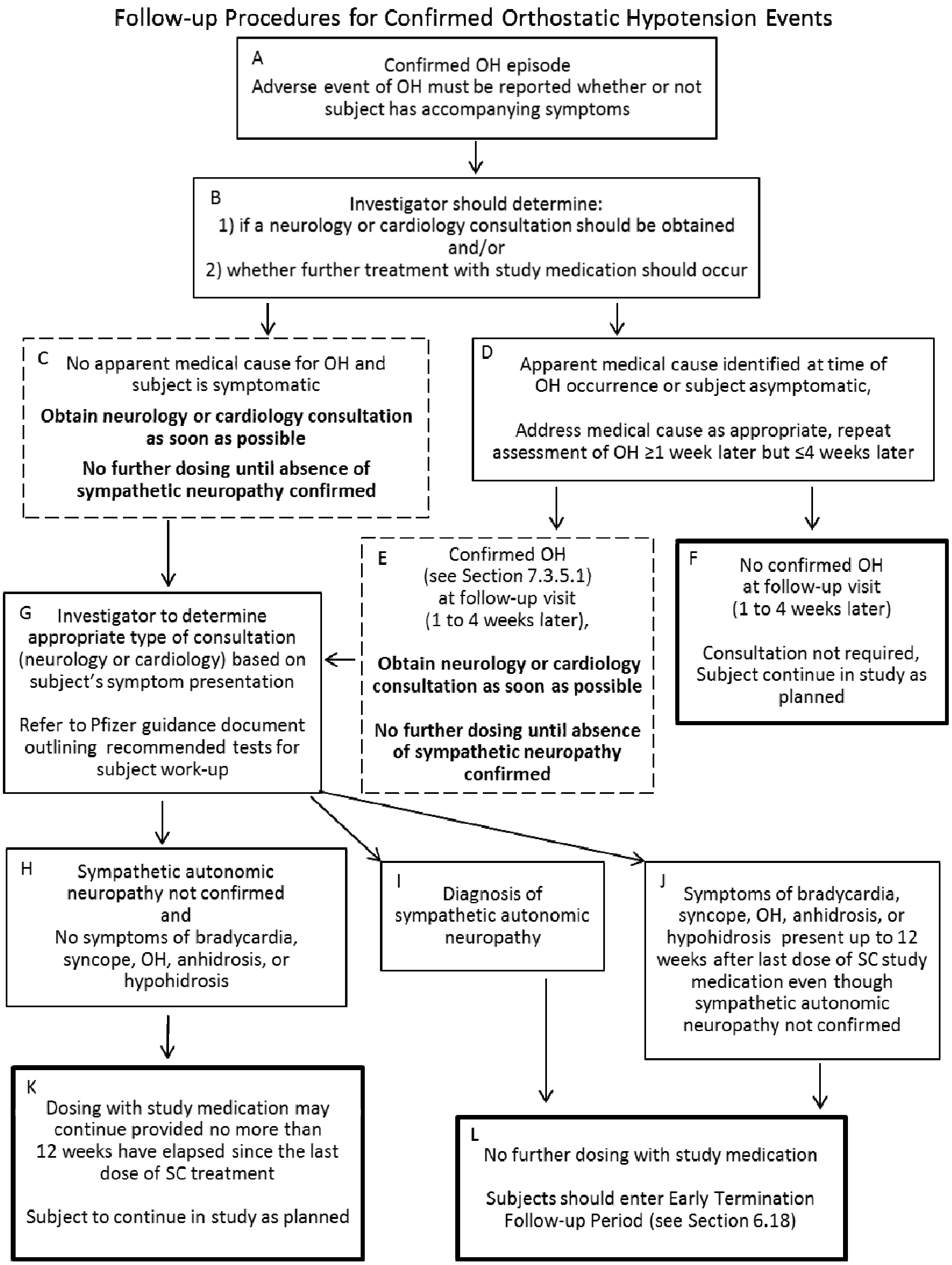
2. If an apparent medical cause is identified at the time the orthostatic hypotension criterion is met or if subject is asymptomatic, the subject should have a repeat assessment of orthostatic hypotension performed at least 1 week later but not more than 4 weeks later. During this time the Investigator should attempt to address the underlying medical cause of the orthostatic hypotension. If confirmed orthostatic hypotension (as defined in Section 7.3.5.1) 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 7.3.6 for ECG criteria for bradycardia), syncope, orthostatic hypotension (as described above and in boxes C and E of flow diagram Figure 2), anhidrosis or hypohidrosis should be further evaluated for the presence of sympathetic autonomic neuropathy by a cardiologist or neurologist as soon as possible.

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

These subjects should not be dosed with SC study medication until the absence of sympathetic autonomic neuropathy has been confirmed. Subjects who are not deemed to have a sympathetic autonomic neuropathy based on this evaluation can continue the study provided no more than 12 weeks have elapsed since the last dose of SC treatment (Boxes H and K of flow diagram Figure 2). However, if the subject is still symptomatic with bradycardia, syncope, orthostatic hypotension, anhidrosis or hypohidrosis up to 12 weeks after the last dose of SC treatment, s/he should not receive additional study medication; even if a sympathetic autonomic neuropathy has not been confirmed (Boxes J and L of flow diagram Figure 2), and will enter the Early Termination Follow-up period (refer to Section 6.20). Subjects found to have a sympathetic autonomic neuropathy (Boxes I and L of flow diagram Figure 2), should not receive additional study medication and will enter the Early Termination Follow-up period (see Section 6.20).

Figure 2. Follow up Procedures for Confirmed Orthostatic Hypotension Events



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

On a weekly basis beginning at the Initial Pain Assessment Period and through Week 80 of the study, the subject will be asked via the IRT if he/she experienced new onset or increased pain in a major joint (refer to Section 7.3.2). If a subject responds that he/she has experienced new onset or increased pain in a major joint (post-baseline), the subject will be asked to rate his/her pain in that joint on the same 11-point numeric rating scale, using a 24-hour recall and will be asked to rate his/her pain in that joint for the remainder of the study.

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

At each study visit, systematic site review of the joint 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 osteoarthritis symptoms will be evaluated by the site personnel. An assessment of the subjects' general health and major joints for any changes in their joint 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. Magnetic Resonance Imaging (MRI) scans will not be required but may be obtained if warranted for diagnostic purposes. If warranted, the subject should be referred to an orthopedic surgeon for evaluation.

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

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 (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 (see Section 6.20).

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 (see Section 6.20).

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 subjects undergoing total joint replacement for any reason, all images and other source documentation will be provided to the blinded tanezumab Adjudication Committee for review and adjudication of the event. The Adjudication Committee's assessment of the event will represent the final classification of the event (refer to Appendix 13).

The Central Reader will review the Week 24 knee X-rays for evidence of radiographic progression of osteoarthritis. The Central Reader will identify subjects entering the study with asymptomatic knee osteoarthritis Kellgren Lawrence Grade 2 who progress to Kellgren Lawrence Grade ≥3 at Week 24. These subjects should be discontinued from tanezumab treatment and entered in the Early Termination Follow-up phase. Unless the Central Reader determines the subject has developed a joint condition that would warrant further evaluation by the Adjudication Committee such as rapidly progressive osteoarthritis, subchondral insufficiency fractures, spontaneous osteonecrosis of the knee (SPONK), primary osteonecrosis or pathological fracture, the images will not be further reviewed by the Adjudication Committee.

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 6.20.2. The follow up will be conducted as part of a substudy if the total joint replacement occurs before the last subject enrolled in Study A4091059 has completed the treatment period. Subjects undergoing total joint replacements after the last subject completes the treatment period may be followed in a separate protocol (Study A4091064).

7.5. Pharmacokinetics (PK) and Pharmacodynamics (PD)

7.5.1. Plasma for Analysis of Tanezumab

Blood samples for the assessment of the PK of tanezumab will be collected Baseline (Day 1; pre-dose) and at Weeks 2 and 4 (in approximately 30% of subjects randomized at selected sites), Week 8 (pre-dose), Week 16 (pre-dose), Week 32 (predose), Week 48 (predose), Week 56, and Week 64. If a subject terminates prior to Week 56, PK will be determined at approximately 8 and 16 weeks after the last SC dose was administered (as described in Section 6.20, Early Termination).

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.

7.5.2. Nerve Growth Factor (NGF) for Pharmacodynamic Analyses

Blood samples will be collected for the assessment of NGF. NGF can exist in different forms including, but not limited to, NGF bound to drug or not bound to drug, NGF bound to soluble p75, and proNGF. Blood volume collected may limit the number of NGF assessments to 3 to 4 NGF endpoints including a measure of total NGF (sum of all NGF forms). The final set of NGF forms, including total NGF, that will be measured will depend on the availability of the analytical assay that can reliably measure the NGF concentration. The time points of NGF sample collection will be at Baseline (Day 1; pre-dose), at Weeks 2 and 4 (in approximately 30% of subjects randomized at selected sites), Week 8 (pre-dose), Week 48 (pre-dose) and at Weeks 56 and 64 (or at Early Termination, as described in Section 6.20). If subjects terminate prior to Week 56, NGF will be determined at approximately 8 and 16 weeks after the last SC dose was administered (or at Early Termination, as described in Section 6.20).

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.

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 will be provided to the Investigator site prior to initiation of the study.

7.6. Biomarkers

7.6.1. Serum Biomarkers

Blood samples for the assessment of biomarkers that can be modulated by the osteoarthritis condition will be collected at Baseline (Day 1; pre-dose in all subjects).

If possible, the samples should be obtained following a fasting period of at least 8 hours. Fasting status should be recorded on the eCRF.

Currently the measurement of 12 biomarkers are planned: CCI [redacted] This selection of biomarkers could change due to blood volume limitations and/or assay performance issues. OA biomarkers different from the ones listed could be added or substituted if considered informative to further understand the osteoarthritis condition.

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 methods. 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

For the assessment of the cartilage biomarker CCI [redacted], urine samples will be collected at Baseline (Day 1); pre-dose in all subjects.

The urine sample should be collected from the second void of the day or later. If possible, the samples should be obtained at approximately the same time at each study visit and following a fasting period of at least 8 hours in order to control for diurnal variations in the biomarkers. Fasting status should be recorded on the eCRF. 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.

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 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 DNA (deoxyribonucleic acid), RNA (ribonucleic acid), 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 badge-swipe. 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 for the purposes described here and in the informed consent document/patient 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/patient information sheet that their results will not be given to them, 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_2 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/patient 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 trial, 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 this section; the biospecimens specified in the Markers of Drug Response section will be used. Subjects may still participate in the clinical trial if they elect not to allow their Banked Biospecimens to be used for the additional purposes described in this Section.

7.8. Other Assessments

7.8.1. PainDETECT

The painDETECT questionnaire was developed with the aim of detecting neuropathic pain components in pain patients, especially in chronic low back pain patients. The questionnaire was developed and validated in a prospective, multicenter study and subsequently applied to approximately 8000 low back pain patients.[45] It is a reliable screening tool with high sensitivity and predictive accuracy and can be used to determine the prevalence of neuropathic pain components in low back pain patients. The painDETECT questionnaire will be administered at Baseline. Refer to Appendix 12 for the painDETECT questionnaire.

7.8.2. NIH Pain Consortium Chronic Low Back Pain Minimum Dataset

Subjects will complete a subset of the questions from the National Institutes for Health (NIH) Pain Consortium Chronic low Back Pain Minimum Dataset at Baseline, Weeks 16 and 56 (and at Early Termination Visit 1, as described in Section 6.20.1.1). The NIH Pain Consortium Chronic Low Back Pain Minimum Dataset has been developed by an NIH task force with the objective to standardize the key data collected in clinical trials to facilitate comparisons across clinical trials.[43] The subset of the NIH Pain Consortium Chronic Low Back Pain Minimum Dataset selected for this study will include measures of pain duration, pain intensity, pain interference, and physical function. A combination of items assessing pain intensity, pain interference with normal activities and physical function create an impact score (range 8-50), where a higher score indicates greater impact. A score of 8-27 indicates a mild impact of chronic low back pain on the subject, 28-34 a moderate impact, and ≥35 a severe impact.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered adverse events (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 adverse event and to assess whether it meets the criteria for classification

as a serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the adverse event. The Investigator is required to assess causality. Follow-up by the Investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the Investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

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

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

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

8.3. Definition of an Adverse Event

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

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

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

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

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error 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 AE, as determined by the investigator, the medication error is captured on the medication error version of the adverse event (AE) page and, if applicable, any associated AE(s) are captured on an AE CRF page.

8.5. Abnormal Test Findings

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

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or

- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the Investigator or sponsor.

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

8.6. Serious Adverse Events

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

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

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

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

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

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

- a life-threatening illness, even if temporary in nature;
- a permanent impairment of a body function or permanent damage to a body structure;

- a condition necessitating medical or surgical intervention to prevent the above 2 bulleted items;

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

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

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

8.6.1. Protocol-Specified Serious Adverse Events

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

8.6.2. Potential Cases of Drug-Induced Liver Injury

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

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

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

- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the upper limit of normal, 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 ≥2 times the baseline values and ≥3 X ULN, or ≥8 X ULN (whichever is smaller).

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

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/International normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

8.7. Hospitalization

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

Hospitalization does not include the following:

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

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself a serious adverse event. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical exam);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical adverse event (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical adverse event;
- Pre-planned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic 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 adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

8.8. Severity Assessment

If required on the adverse event case report forms (CRFs), the Investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the adverse event. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with 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 serious adverse 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 adverse event; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the Investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see the Section on Reporting Requirements). If the Investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the Investigator determines that an that 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/unlicenced 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 having been directly 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 has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the Investigator must submit this information to the Pfizer Drug Safety Unit on a Serious Adverse Event (SAE) Report Form and 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 adverse event has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

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

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

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as serious adverse events when the Investigator assesses the infant death as related or possibly related to exposure to the investigational product.

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

8.10.1. Additional Post-Natal Follow-up

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

8.11. Occupational Exposure

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

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

8.12. Withdrawal Due to Adverse Events (See Also Section on Subject Withdrawal)

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

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

8.13. Eliciting Adverse Event Information

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

8.14. Reporting Requirements

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

8.14.1. Serious Adverse Event Reporting Requirements

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

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available adverse event 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 adverse event.

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

8.14.2. Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the adverse event page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the adverse event CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example,

the same adverse event term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Medical Device Reporting Requirements

All medical device complaints regardless of whether the medical device complaint is associated with an AE will be collected on the applicable pages within the CRF. This includes potential incidents or malfunctions associated with the use of a medical device product. An incident or malfunction is an event that might have led to death or serious deterioration in health, or if it occurred again might have led to death or serious deterioration in health.

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

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

8.14.4. Sponsor's Reporting Requirements to Regulatory Authorities

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 minimum sample size of approximately 400 subjects per treatment group are needed to provide at least 80% power to achieve statistical significance (at the 5% two-sided level) for both comparisons of tanezumab 10 mg and 5 mg versus placebo as well as the comparison of tanezumab 10 mg versus active comparator in the primary endpoint, Change from Baseline to Week 16 in the average LBPI score. Since placebo subjects reaching Week 16 response criteria will be switched to tanezumab treatment only, in order to balance subject exposure during the safety phase of the trial (post Week 16) the number of subjects randomized at Baseline to the active comparator group will be increased to approximately 600. The total sample size will be approximately 1800 subjects.

The assumed treatment differences from placebo for this calculation are -0.5, -0.9 and -0.4 for tanezumab 5 mg, tanezumab 10 mg and active comparator, respectively. The within group standard deviation was assumed to be 2.4 based on a prior chronic low back pain study (A4091012).

In order to gain adequate long term safety data in the chronic low back pain population, it is desirable to have approximately 100 subjects per group achieve 56 weeks of exposure. It is anticipated that, at most, 70% of subjects entering the Long-Term Safety and Efficacy Phase of the study (at Week 16) will complete an additional 40 Weeks. Thus, if the observed number of subjects meeting the Week 16 response criteria does not reach ≥400 at the time the total number of subjects randomized at Baseline reaches 1600, plans will be made to extend enrollment beyond the minimum sample size such that at least 450 subjects are enrolled in the Long-Term Safety and Efficacy Phase of this study.

9.2. Efficacy Analysis

9.2.1. Analysis of Primary Endpoint

The primary efficacy endpoint is change from Baseline to Week 16 in average LBPI score specifically for the comparison of tanezumab versus placebo. The analysis of change from Baseline to Week 16 in average LBPI will include all treatment groups; therefore the analysis of the corresponding key secondary endpoint for the comparison of tanezumab vs tramadol will be included in this analysis. All text in this section relates to both sets of comparisons (even when only primary endpoint is mentioned).

The primary efficacy population will be the ITT population, defined as all randomized subjects who received SC study medication (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 primary efficacy endpoint will be analyzed using an ANCOVA model, with model terms for Baseline score 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. First, the tanezumab 10 mg group will be tested versus placebo, and if statistically significant ($p \leq 0.05$) then the tanezumab 5 mg group will be tested versus placebo. This testing procedure will maintain the Type I error to 5% or less.

An additional (main effects ANCOVA) analysis will use a per-protocol analysis set, which will exclude subjects who are major protocol deviators.

The primary analysis of the primary endpoint will use multiple imputation for missing data, to account for uncertainty around the subject response. The basis for imputing missing values will be dependent on the reasons for missing data. 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 of the subject's Baseline efficacy value and the standard deviation (over all treatment groups) of the observed efficacy data at Week 16. For subjects with missing data for any other reason, imputation will be based on sampling from a normal distribution using a mean value of the subject's last observed efficacy value and standard deviation (over all treatment groups) of the observed efficacy data at Week 16. Imputed values will be truncated at 0 and 10. One hundred imputation samples will be used, and the ANCOVA model described above will be used for each imputation dataset. The final results will be calculated using the combined sets of results from each imputation dataset analysis.[35]

Additional analyses will explore the sensitivity of the primary analysis results to missing data. The first analysis will use the same main effects ANCOVA model as described above, but with Last Observation Carried Forward (LOCF) single imputation for missing data. The second analysis will use the same main effects ANCOVA model as described above, but with Baseline Observation Carried Forward (BOCF) single imputation for missing data. The third analysis will use Mixed Model for Repeated Measurements (MMRM) utilizing all observed data up to and including Week 16.

All analyses will show estimates of the treatment group means and differences between treatment groups with corresponding standard errors, 95% confidence intervals and p-values (for treatment group differences).

9.2.2. Analysis of Secondary Endpoints

Unless otherwise stated, all analyses for the comparison of tanezumab versus placebo will be for timepoints up to Week 16, and for the comparison of tanezumab versus tramadol will be for timepoints up to Week 56. Summaries of data will be up to Week 16 for placebo, and up to Week 80 for the tanezumab and tramadol treatment groups.

For the key secondary objective of tanezumab versus placebo for the change from Baseline to Week 16 for the RMDQ, these treatment comparisons will be made conditional on the primary efficacy comparisons. In particular, tanezumab 10 mg versus placebo for RMDQ will be tested if tanezumab 10 mg versus placebo for average LBPI is significant ($p \leq 0.05$), and then tanezumab 5 mg versus placebo for RMDQ will be tested if both (1) tanezumab 10 mg versus placebo for RMDQ and (2) tanezumab 5 mg versus placebo for average LBPI are significant ($p \leq 0.05$). The same step down testing strategy used for the primary endpoint will be employed for comparisons of tanezumab to tramadol treatment for the key secondary endpoint of change from Baseline to Week 16 for the average LBPI. These comparisons will be made conditional on the primary efficacy comparisons. Use of the step-down testing will ensure the type I error is maintained to 5% or less within each of the key secondary objectives. The key secondary endpoint of RMDQ will be analyzed using an ANCOVA model, with model terms for Baseline score, Baseline LBPI score, treatment group, and study site as a random effect.

Secondary endpoints will examine the change from Baseline to additional timepoints prior to Week 16 in LBPI score (ie, Weeks 2, 4, 8 and 12), using the multiple imputation for missing data procedure and analysis described above for the comparisons of tanezumab versus placebo and tramadol. The same analyses will be undertaken for the change from Baseline to Weeks 24, 32, 40, 48 and 56 in average LBPI for the comparisons of tanezumab versus tramadol only.

Other secondary endpoints include the RMDQ total score, the Patient's Global Assessment of Low Back Pain, and the seven BPI-sf measures. The analysis of these endpoints, as change from Baseline to Weeks 2, 4, 8 and 16 (for tanezumab versus placebo and tramadol comparisons) and to Weeks 24, 32, 40, 48 and 56 (for tanezumab versus tramadol comparisons) will use the same ANCOVA analysis as described above for the primary endpoint with multiple imputation for missing data. The model for RMDQ and Patient's Global Assessment of Low Back Pain analysis will also include Baseline LBPI score.

Subject response endpoints of improvement in the average LBPI score and the RMDQ score of ≥30, 50, 70 and 90%, improvement in the Patient's Global Assessment of Low Back Pain ≥2 points and the Chronic Low Back Pain Responder Index will be analyzed at Weeks 2, 4, 8, 12 (average LBPI response only) and 16 (for tanezumab versus placebo and tramadol comparisons) and to Weeks 24, 32, 40, 48 and 56 (for tanezumab versus tramadol comparisons) using logistic regression for binary data. The model for the analysis of the responders based on average LBPI score and Chronic Low Back Pain Responder Index will include model terms for Baseline average LBPI score and treatment group. The model for the analysis of the Patient's Global Assessment of Low Back Pain responders will include the Baseline PGA score, Baseline average LBPI score and treatment group. These analyses will be run using both BOCF and LOCF imputation for missing data. In addition, in order to closely match the primary imputation analysis, a mixed BOCF/LOCF imputation for response endpoints will be used. In this analysis BOCF imputation (ie, a subject would be a non-responder) would be used for missing data due to discontinuation for reasons of 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 Low Back Pain to Weeks 2, 4, 8 and 16 (for tanezumab versus placebo and tramadol comparisons) and to Weeks 24, 32, 40, 48 and 56 (for tanezumab versus tramadol comparisons) will also be analyzed using the Cochran-Mantel-Haenszel test. 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.

The incidence of use of rescue medication and number of days of use will be analyzed for Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48 and 56, and the amount of rescue medication use 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 average LBPI score and treatment group. The number of days and amount of rescue medication (mg dosage of acetaminophen/paracetamol) will be analyzed using the Negative Binomial model, with model terms of Baseline average LBPI score 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 and tramadol will be shown. Imputation for missing rescue medication data will use LOCF only. The incidence and number of days of rescue medication use will be summarized up to Week 64, and the amount of rescue medication taken in a week summarized up to Week 16.

The incidence of and time to withdrawal due to lack of efficacy will also be analyzed for discontinuations up to Week 16 (for comparisons of tanezumab versus placebo and tramadol) and up to Week 56 (for comparisons of tanezumab versus tramadol). 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, 2, 5, 10 and 25 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 average LBPI score and treatment group.

Cumulative average LBPI and RMDQ response at Weeks 16, 24 and 56 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 both LOCF and BOCF imputation. Imputation with BOCF for subjects with missing data at that timepoint will lead to subjects being assessed as non-responders for the response endpoint.

A two-way table showing number and percentage of subjects will summarize the response for each dimension (item) for the EQ-5D-5L at Baseline versus Weeks 8, 16, 24, 40, 56, and 64. These summary tables will be shown by treatment group. In addition, the EQ-5D-5L overall health utility score will be summarized for each treatment and for each time point assessed.

Summaries of the change from Baseline to Weeks 16, 56, and 64 in the WPAI:LBP impairment scores will be shown by treatment group.

All data from TSQM and mPRTI will be summarized by visit. The domains of the TQSM and items of the mPRTI (patient willingness to use drug again; patient preference of drug versus prior treatment) will be analyzed using the Cochran-Mantel-Haenszel (CMH) test at both Weeks 16 and 56. Summaries and change from Baseline in the NIH Pain Consortium Chronic Low Back Pain Minimum Dataset responses by question and domain will be reported by treatment group for Baseline, Week 16 and 56. Categorical summaries of severity in the pain impact domain and other domains may be reported by treatment for Baseline, Weeks 16 and 56. The HCRU data will be reported as outlined in the SAP.

Summaries of data after Week 16 will show the subjects receiving tanezumab in 4 separate groups: (1) placebo→tanezumab 5 mg (those subjects initially randomized to placebo and switched to tanezumab 5 mg at Week 16), (2) placebo→tanezumab 10 mg (those subjects initially randomized to placebo and switched to tanezumab 10 mg at Week 16), (3) tanezumab 5 mg (those subjects initially randomized to tanezumab 5 mg and continuing with tanezumab 5 mg after Week 16), (4) tanezumab 10 mg (those subjects initially randomized to tanezumab 10 mg and continuing with tanezumab 10 mg after Week 16), as well as tanezumab groups by dose received after Week 16. All assessments of change from baseline and treatment response will be made according to the Baseline at the beginning of the study. Two separate analyses will be made for comparisons of tanezumab dose groups versus tramadol for time points after Week 16. The first analysis will include all subjects (ie, subjects who received placebo prior to Week 16 and were switched to one of the two tanezumab dose groups will be included in the respective tanezumab dose group). The second analysis will exclude subjects who received placebo prior to Week 16 and were randomized to one of the two tanezumab dose groups at Week 16 (ie, this analysis will only include subjects whose treatment was constant throughout the study).

Any additional sensitivity analyses of secondary efficacy endpoints to explore the potential difference between tramadol dosing post Week 16 in European subjects vs.subjects outside of Europe will be specified in the statistical analysis plan.

Any efficacy data collected at an Early Termination visit will be excluded from summary and analyses of efficacy with the following exception: Any efficacy data collected at the Early Termination visit for subjects that have discontinued the study early, and the observations are within 10 weeks after the last dose (8 weeks plus a window of 2 weeks) can be included in the efficacy summaries and analyses for the appropriate efficacy window in which the data falls.

9.3. Analysis of Safety Endpoints

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

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

- Separate adverse event summaries by treatment group for adverse events of decreased sympathetic function will be conducted. More specifically, adverse events with the following preferred terms will be considered to represent adverse events of decreased sympathetic function: Blood pressure orthostatic decreased, bradycardia, dizziness postural, heart rate decreased, orthostatic hypotension, presyncope, sinus bradycardia, syncope, anhidrosis, hypohidrosis, abdominal discomfort, diarrhea, early satiety, fecal incontinence, nausea, vomiting, ejaculation delay, ejaculation disorder, ejaculation failure, hypertonic bladder, micturition urgency, nocturia, urinary frequency, urinary hesitation, urinary incontinence, respiratory distress and respiratory failure. If necessary, this list of preferred terms may be adjusted for updates made to the MedDRA dictionary versions used for reporting.

- In addition to summaries of adverse events considered to represent adverse events of decreased sympathetic function noted above, adverse events of syncope, bradycardia, orthostatic hypotension, anhidrosis, or hypohidrosis are designated as adverse events of interest that will be reviewed by the unblinded 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 Neuropathy Impairment Score (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 will be summarized, and analyzed using a Cochran-Mantel-Haenszel test. The change from Baseline to each study visit (using LOCF for missing data), and to Worst (largest) change from Baseline (over all post-Baseline visits) will be summarized.
- The neurological consultation data will be summarized all subjects, and for subjects with adverse events of abnormal peripheral sensation, which are described in the Neurological Examination Section (Section 7.3.9) above. The "conclusion from the neurological examination" data will be summarized for each timepoint, and as well as 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 will be shown by number of subjects treated and patient-years of exposure (treatment plus follow-up periods), for individual treatment groups and differences between tanezumab treatment groups and the tramadol treatment group. The risk ratio and risk difference with 95% Confidence intervals will be calculated for the comparisons of each tanezumab group versus the tramadol group, as well as significance tests for each treatment comparison. The time to each event will be summarized, and (where there are sufficient numbers of subjects) Kaplan-Meier estimates of the time to event will be produced, together with an analysis of each tanezumab treatment group versus the tramadol group using the log-rank test.
- The incidence of subjects with any of the joint safety adjudication outcomes of rapidly progressive osteoarthritis (type-2), subchondral insufficiency fracture (or SPONK), primary osteonecrosis, or pathological fracture will be analyzed as described above. In addition the same analysis will be performed for the individual events of all-cause Total Joint Replacements, and adjudicated outcomes of rapidly progressive osteoarthritis (type 1, type 2 and both types 1 and 2 combined), subchondral insufficiency fracture (or SPONK), primary osteonecrosis and pathological fracture.
- A listing of the subjects who develop anti-tanezumab antibodies after treatment for each dose, and the proportion of subjects who develop anti-tanezumab will be summarized for each dose.
- The PK profile will be examined for subjects with anti-tanezumab antibodies.
- Individual subjects with positive ADA results will be evaluated for potential impact on the individual's pharmacokinetic, efficacy and safety profile.

9.3.1. Analysis of Total Joint Replacement Substudy

All analyses will be descriptive in nature (see also Section 109 of the substudy protocol).

9.4. Analysis of Other Endpoints

9.4.1. Pharmacokinetic Data

Tanezumab concentrations will be measured to support the development of a SC population PK model that allows for the prediction of the tanezumab concentration over time in individuals. In addition tanezumab concentrations will be measured to inform the immunogenicity profile of tanezumab.

PK samples at Weeks 2 and 4 will only be collected in approximately 30% of subjects randomized at selected sites.

The following reporting of PK data will be done:

- A listing of all plasma tanezumab concentrations sorted by subject, dose and nominal time post dose. The listing of concentrations will also include the actual times post dose.
- A descriptive summary of the plasma tanezumab concentrations based on nominal time post dose for each dose.

9.4.2. Pharmacodynamic (NGF) Data

Nerve Growth Factor data analyses will be conducted according to the NGF analysis plan.

9.4.3. Biomarker Data

Biomarker data analysis will be conducted according to the tanezumab biomarker analysis plan.

9.5. External Adjudication Committee

A blinded Adjudication Committee consisting of external experts in orthopedic surgery, rheumatology, orthopedic pathology, or radiology with expertise in patients with end stage osteoarthritis and osteonecrosis will be convened. The Adjudication Committee will have written operating procedures and a Charter, including a specific description of the scope of their responsibilities. In general, the Adjudication Committee will be asked to review all possible or probable joint-related safety events identified by the Central Reader, total joint replacement as well as investigator-reported adverse events of osteonecrosis, rapidly progressive osteoarthritis, subchondral insufficiency fracture (spontaneous osteonecrosis of the knee [SPONK]) or pathologic fracture. Adverse events related to joint safety that the investigator or sponsor considers medically important may also be reviewed by the Adjudication Committee. These will include, but will not be limited to events identified for adjudication by the Central Reader (see Section 7.4.5).

Prior to the Adjudication Committee's review of a given event, the Committee will be provided with blinded, available source documentation of progress reports from the Investigator, orthopedic consult reports, operative reports, radiology reports, pathology reports, X-ray images, MRI images, and pathology specimens for review. Copies of all

relevant clinical information including the items listed above should be provided to Pfizer or its designee for review by the external Adjudication Committee. Copies of the information should include the study number, site number and subject number, but it should not include the subject's name or initials.

The external Data Monitoring Committee (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

An independent, external DMC has been instituted for the tanezumab clinical program. This committee will be composed of at least one rheumatologist, neurologist, statistician, and epidemiologist. The 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 DMC during review of unblinded safety data. The DMC will have written operating procedures and a Charter, including a specific description of the scope of their responsibilities.

The 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 (See Section 9.3), an urgent, ad hoc assessment of the events will be made by the DMC.

Any recommendations made by the 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.

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 Data Monitoring Committee (DMC). The 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 DMC will be conducted. The 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 or active control -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 DMC.

If the protocol-based stopping rule is triggered, the 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 DMC.

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

- Consideration of relationship of study medication to the adverse event;
- Consideration of whether similar adverse events are occurring in other tanezumab studies with similar subject populations;

- Dosage of tanezumab (5 mg or 10 mg) and distribution of adverse events across tanezumab dose arms;
- Possible differences in the baseline demographics between study treatment groups;
- Use of concomitant medications;
- Possible differences in baseline medical history and/or co-morbidities;
- Study medications other than tanezumab;
- 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 study drug 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 DMC will determine whether the dosing suspension should be triggered. Subsequently the 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 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 Data Monitoring Committee.

The protocol (or treatment group) stopping rule has three components; the difference in the number of subjects with an adjudicated joint safety event, the exposure-adjusted risk difference (RD) and the exposure adjusted risk ratio (RR) between each tanezumab treatment group and the tramadol PR treatment group. The exposure-adjusted RD will be calculated as the difference in the ratios of the number of subjects with an adjudicated joint safety event divided by exposure (patient-years) between each tanezumab group and the comparator group. The exposure-adjusted RR will be similarly calculated using the ratio of exposure adjusted event rates (number of subjects with an adjudicated joint safety event divided by exposure) for each tanezumab group relative to the comparator group. The exposure will be calculated as the combined treatment and follow-up periods.

If the RD [redacted], and the RR is [redacted] and the difference in the number of subjects with adjudicated events joint safety events for any tanezumab treatment group versus the comparator treatment group, the

protocol-based stopping rule will be triggered. If the protocol-based stopping rule is triggered, the 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 Data Monitoring Committee.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is 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.

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.

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

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

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

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

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the Investigator according to International Conference on Harmonisation (ICH), local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

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

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

12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

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

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

12.2. Ethical Conduct of the Study

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

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

12.3. Subject Information and Consent

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

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

The informed consent 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 by the sponsor, approved by the IRB/EC 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.

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 ethics committees and Investigator databases may be used as recruitment procedures.

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/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of tanezumab at any time.

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

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

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

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

<u>www.clinicaltrials.gov</u>

Pfizer posts clinical trial US Basic Results on 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.

<u>EudraCT</u>

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

www.pfizer.com

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

15.2. Publications by Investigators

Pfizer has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) 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 (other than the Study results themselves) before disclosure.

If the Study is part of a multi-centre study, Investigator agrees that the first publication is to be a joint publication covering all centers. 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, Investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the Study, 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 Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

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Appendix 1. Quebec Task Force Classification

TFC Category	Definition		Duration of Symptoms		Work Status
1	Pain without radiation				
2	Pain with proximal radiation (above the knee)	}	a (<7 days)	}	Working or not working
3	Pain with distal radiation (below the knee)		b (7 days to 7 weeks)		
4	Pain with distal radiation and neurologic signs		c (>7 weeks)		
5	Presumptive compression of a spinal nerve root on a simple roentgenogram				
6	Compression of a spinal nerve root confirmed by specific imaging techniques				
7	Spinal stenosis				
8	Post surgical 1–6 mo after the intervention				
9	Post surgical >6 mo after the intervention				
10	Chronic pain syndrome				Working or not working
11	Other diagnoses				

Appendix 2. American College of Rheumatology (ACR) Classification Criteria for Osteoarthritis

OA Hip Criteria[22]

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

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

ESR testing may be conducted at the local laboratory.

1986 OA Knee Criteria[22]

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

Meets criteria 1, 2 and 3:

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

Appendix 3. 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;[46] a sixth category was later added. See also :http://www.asahq.org/Home/For-Members/Clinical-Information/ASA-Physical-Status-Classification-System.

These are:

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

Appendix 4. Half-Lives of Prohibited Prior and Concomitant Medications

Use of prohibited analgesics except acetaminophen/paracetamol is prohibited up to Week 16 beginning 48 hours prior to the start of the Initial Pain Assessment Period (the five days prior to Randomization/Baseline) 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. Starting at Week 16, analgesics for low back pain may be used, with the **exception of NSAIDs,coxibs, and opioids.** NSAIDs, coxibs, and opioids are prohibited through Week 64 or until 16 weeks after the last dose of SC study medication in the case of subjects who early terminate. Note that a stable regimen of aspirin taken for cardiac prophylaxis at a dose of ≤325 mg/day is permitted throughout the study.

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

HALF-LIVES OF NSAIDs AND OTHER ANALGESICS		
Analgesic	**Half-life (hours)**	**Minimum Washout Period**
Aspirin ≥325 mg/day	0.25	2 days
Azapropazone	15.0	4 days
Bromfenac	1.3-3.1	2 days
Capsaicin (cream, ointments, patches)	2.0	2 days
Carprofen	12.0	3 days
Celecoxib	11.0	3 days
Codeine	3.5	2 days
Diclofenac gels	1.9	2 days
Diclofenac	1.1	2 days
Diclofenac/misoprostol	2.4-9.0	2 days
Diflunisal	13.0	3 days
Dipyrone	2.0-5.0	2 days
Etodolac	6.0	2 days
Fenbufen	11.0	3 days
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

HALF-LIVES OF NSAIDs AND OTHER ANALGESICS		
Analgesic	**Half-life (hours)**	**Minimum Washout Period**
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

Half-Lives of Muscle Relaxants

Use of any muscle relaxant is prohibited during the Treatment Period up to Week 16 starting from the time period within 48 hours prior to the start of the Initial Pain Assessment Period (the five days prior to Randomization/Baseline) or during the period of time prior to the start of the Initial Pain Assessment Period that is ≤5x the half-life of the particular muscle relaxant used, whichever is greater.

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

HALF-LIVES OF MUSCLE RELAXANTS		
Muscle Relaxant	**Half-life (hours)**	**Minimum Washout Period**
Baclofen	3.0-6.8	2 days
Carisoprodol	8.0	2 days
Clorzoxazone	1.1	2 days
Cyclobenzaprine	18.0-33.0	7 days
Dantrolene	8.7	2 days
Diazepam	20.0-54.0	12 days
Eperisone	1.6-1.8	2 days
Flupirtine	7.0-10.0	3 days
Merobamate	9.0-11.0	3 days
Methocarbamol	0.9-2.0	2 days
Metaxalone	2.4-9.2	2 days
Orphenadrine	13.2-20.1	5 days
Tetrazepam	13.0-45.0	10 days
Tizanidine	2.0	2 days

Anti-Depressants

Anti-depressants for the treatment of depression are prohibited within 30 days prior to Screening up to Week 16 with the exception of stable treatment (unchanged for at least 30 days prior to Screening) with selective serotonin reuptake inhibitors (SSRIs). Use anti-depressants for the treatment of low back pain is prohibited during the Treatment Period up to Week 16 starting from the time period within 48 hours prior to the start of the Initial Pain Assessment Period (the five days prior to Randomization/Baseline) or during the period of time prior to the start of the Initial Pain Assessment Period that is ≤5x the half-life of the particular anti-depressant used, whichever is greater.

This excludes from the trial any subjects receiving: tricyclic and related cyclic antidepressants, monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase Type A (RIMAs), serotonin and norepinephrine reuptake inhibitors (SNRIs & NSRIs), and other miscellaneous antidepressants.

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.

PROHIBITED ANTI-DEPRESSANTS	
Tricyclic and Related Cyclic Antidepressants	**Serotonin and Norepinephrine Reuptake Inhibitors**
amitriptyline	venlafaxine
amoxapine	nefazodone
clomipramine	reboxetine
desipramine	atomoxetine
doxepin	duloxetine
imipramine	
maprotiline	**Reversible Inhibitors of Monoamine Oxidase Type A (RIMAs)**
nortriptyline	
protriptyline	brofaromine
trimipramine	moclobemide
Monoamine Oxidase Inhibitors (MAOIs)	**Miscellaneous Antidepressants**
phenelzine	bupropion
selegiline	mirtazapine
tranylcypromine	St John's Wort
	trazodone

Centrally Acting Agents

Other centrally acting agents are allowed with limitations. The use of any sedatives/hypnotics, anxiolytics, tranquilizers, or benzodiazepines is prohibited up to Week 16 unless the subject's prescribed daily dose has remained unchanged throughout the 30 days prior to Screening and will remain unchanged through the Week 16 the study period. Benzodiazepines prescribed as a muscle relaxant are prohibited and must be discontinued via washout. In this case, refer to Half-Lives of Muscle Relaxants.

The following lists are provided for your reference but may not be all-inclusive. Refer to the Physician's Desk Reference for exclusive determination of a particular agent.

Anxiolytics	Sedatives/Hypnotics	Benzodiazepines
alprazolam	amobarbital	alprazolam
buspirone	butabarbital	bromazepam
clonazepam	chlordiazepoxide	chlordiazepoxide
chlordiazepoxide	clorazepate	clonazepam
diazepam	diazepam	clorazepate
doxepin	estazolam	diazepam
halazepam	flurazepam	estazolam
hydroxyzine	lorazepam	flurazepam
lorazepam	mephobarbital	halazepam
meprobamate	midazolam	ketazolam
oxazepam	phenobarbital	lorazepam
trifluoperazine	quazepam	midazolam
	secobarbital	oxazepam
	temazepam	quazepam
	triazolam	temazepam
	zolpidem	triazolam

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.

TNFα inhibitors	
Generic	**Brand**
Adalimumab	Humira
Etanercept	Enbrel
Infliximab	Remicade

Use of live attenuated vaccines (with the exception of Flumist® Influenza Virus Vaccine Live, Intranasal or other inhaled/intranasal live influenza vaccines in regions where these vaccines are approved) 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.

Live attenuated vaccines	
Generic	**Brand**
BCG (for tuberculosis)	Not available in the US
Herpes zoster vaccine	Zostavax
Measles	Attenuvax
Measles, mumps, and rubella (MMR)	MMR
Mumps	Mumpsvax
Oral poliovirus vaccine, oral	OPV (no longer available in the US)
Rotavirus, oral	RotaTeq
Rubella	Meruvax II
Smallpox	Dryvax (Not commercially available in the US)
Typhoid, oral	Vivotif Berna
Varicella zoster	Varivax
Yellow fever	YF-VAX

Appendix 5. Patient Health Questionnaire (PHQ-9)

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 1-9 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.

Patient Health Questionnaire (Version 2.1.0)

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	☐	☐	☐	☐
2. Feeling down, depressed, or hopeless	☐	☐	☐	☐
3. Trouble falling or staying asleep, or sleeping too much	☐	☐	☐	☐
4. Feeling tired or having little energy	☐	☐	☐	☐
5. Poor appetite or overeating	☐	☐	☐	☐
6. Feeling bad about yourself--or that you are a failure or have let yourself or your family down	☐	☐	☐	☐
7. Trouble concentrating on things, such as reading the newspaper or watching television	☐	☐	☐	☐
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	☐	☐	☐	☐
9. Thoughts that you would be better off dead or of hurting yourself in some way	☐	☐	☐	☐

Total Score: ___

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?

Not difficult at all	**Somewhat difficult**	**Very difficult**	**Extremely difficult**
☐	☐	☐	☐

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. Use of the PHQ-9 may only be made in accordance with the Terms of Use available of http://www.pfizer.com.

Appendix 6. Roland Morris Disability Questionnaire (RMDQ)

Instructions:

When your back hurts, you may find it difficult to do some of the things you normally do. This list contains some sentences that people have used to describe themselves when they have back pain. When you read them, you may find that some stand out because they describe you *today*. As you read the list, think of yourself *today*. When you read a sentence that describes you *today*, put a check in the yes box. If the sentence does not describe you, then leave the space blank and go on to the next one. Remember, only check the box if you are sure it describes you today.

Questionnaire:		**YES**
1.	I stay at home most of the time because of my back.	□
2.	I change position frequently to try and get my back comfortable.	□
3.	I walk more slowly than usual because of my back.	□
4.	Because of my back, I am not doing any of the jobs that I usually do around the house.	□
5.	Because of my back, I use a handrail to get upstairs.	□
6.	Because of my back, I lie down to rest more often.	□
7.	Because of my back, I have to hold on to something to get out of an easy chair.	□
8.	Because of my back, I try to get other people to do things for me.	□
9.	I get dressed more slowly than usual because of my back.	□
10.	I only stand for short periods of time because of my back.	□
11.	Because of my back, I try not to bend or kneel down.	□
12.	I find it difficult to get out of a chair because of my back.	□
13.	My back is painful almost all the time.	□
14.	I find it difficult to turn over in bed because of my back.	□
15.	My appetite is not very good because of my back pain.	□
16.	I have trouble putting on my socks (or stockings) because of pain in my back.	□
17.	I only walk short distances because of my back.	□
18.	I sleep less well because of my back.	□
19.	Because of my back pain, I get dressed with help from someone else.	□
20.	I sit down for most of the day because of my back.	□
21.	I avoid heavy jobs around the house because of my back.	□
22.	Because of my back pain, I am more irritable and bad tempered with people than usual.	□
23.	Because of my back, I go upstairs more slowly than usual.	□
24.	I stay in bed most of the time because of my back.	□

Appendix 7. Patient's Global Assessment of Low Back Pain

The patient's response using the 5-point Likert scale of 1 being the best (very good) and a score of 5 being the worst (very poor) will be recorded in the CRF.

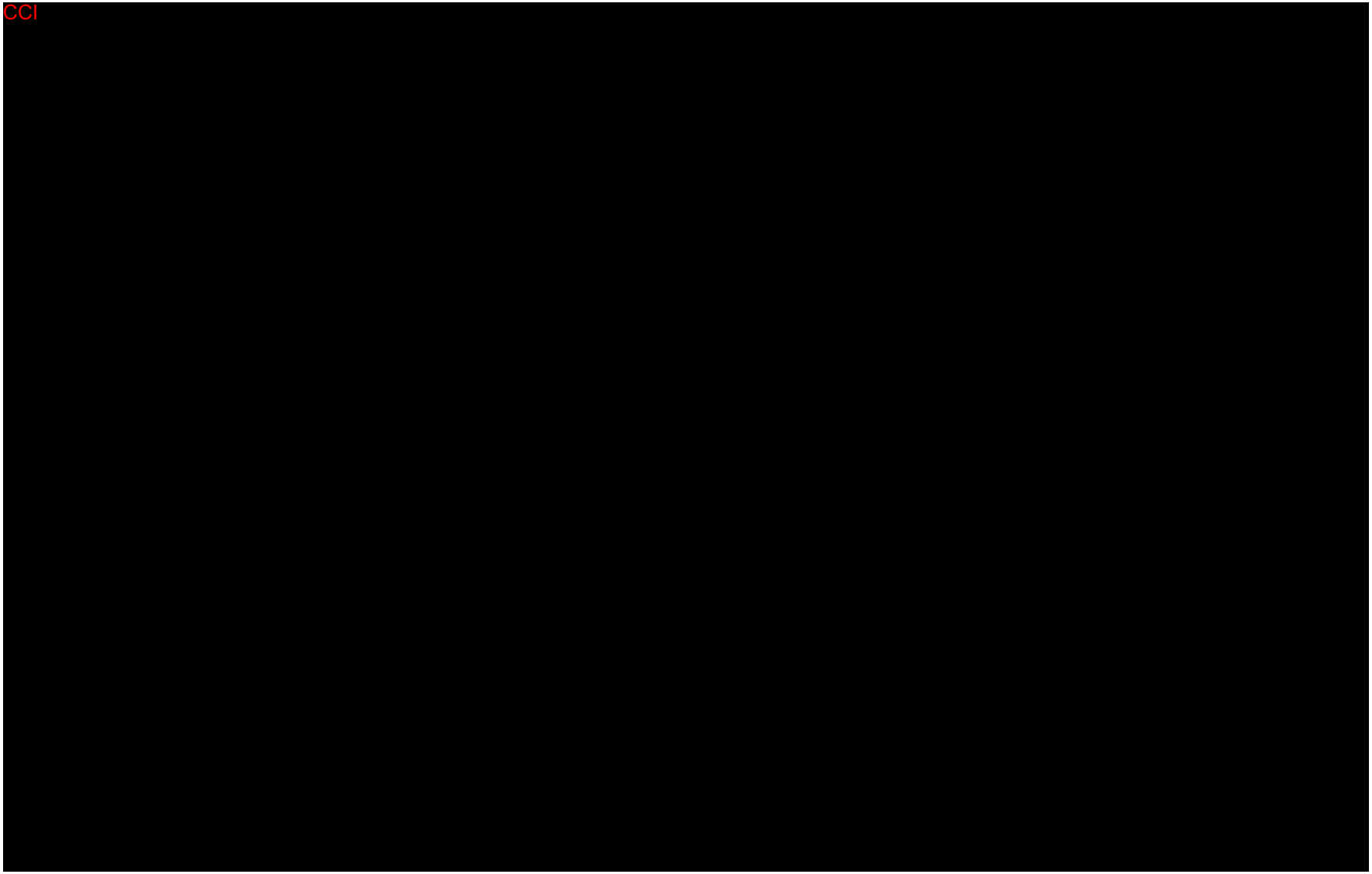
The subjects will answer the following question:

"Considering all the ways your low back pain 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

Appendix 8. Brief Pain Inventory – Short Form (BPI-sf)

CCI



CCI

[redacted]

Appendix 9. Work Productivity and Activity Impairment Questionnaire: Low Back Pain (WPAI:LBP)

The following questions ask about the effect of your LOW BACK PAIN 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 LOW BACK PAIN? *Include hours you missed on sick days, times you went in late, left early, etc., because of your LOW BACK PAIN. 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).*

5. During the past seven days, how much did your LOW BACK PAIN affect your productivity while you were working?

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 LOW BACK PAIN affected your work only a little, choose a low number. Choose a high number if LOW BACK PAIN affected your work a great deal.

Consider only how much LOW BACK PAIN affected productivity while you were working.

LOW BACK PAIN had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	LOW BACK PAIN completely prevented me from working

CROSS A NUMBER

6. During the past seven days, how much did your LOW BACK PAIN affect your ability to do your regular daily activities, other than work at a job?

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 LOW BACK PAIN affected your activities only a little, choose a low number. Choose a high number if LOW BACK PAIN affected your activities a great deal.

Consider only how much LOW BACK PAIN affected your ability to do your regular daily activities, other than work at a job.

LOW BACK PAIN had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	LOW BACK PAIN completely prevented me from doing my daily activities

CROSS A NUMBER

WPAI:LBP V2.0 (US English)

Appendix 10. Subject Daily/Weekly Assessments of Low Back Pain

Daily and Weekly Assessments

Subjects will use IRT to complete questionnaires recording subject average daily pain low back pain intensity (LBPI) scores with a 24-hour recall. The LBPI score will be captured once daily from the Initial Pain Assessment Period up to Week 16, and once weekly from Week 16 to Week 64, in the evening if possible.

Low Back Pain Intensity (from the beginning of the Initial Pain Assessment Period to Week 64):

Low Back Pain Intensity

"Select the number that best describes average low back pain in the past 24 hours."

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Possible Pain

If an IRT is used, additional instructional language may need to be added to the question such as "Using a scale from 0 to 10, with 0 meaning no pain and 10 meaning worst possible pain; please enter the number that best describes your average low back pain in the past 24 hours."

Appendix 11. Euro Quality of Life Health State Profile (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

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

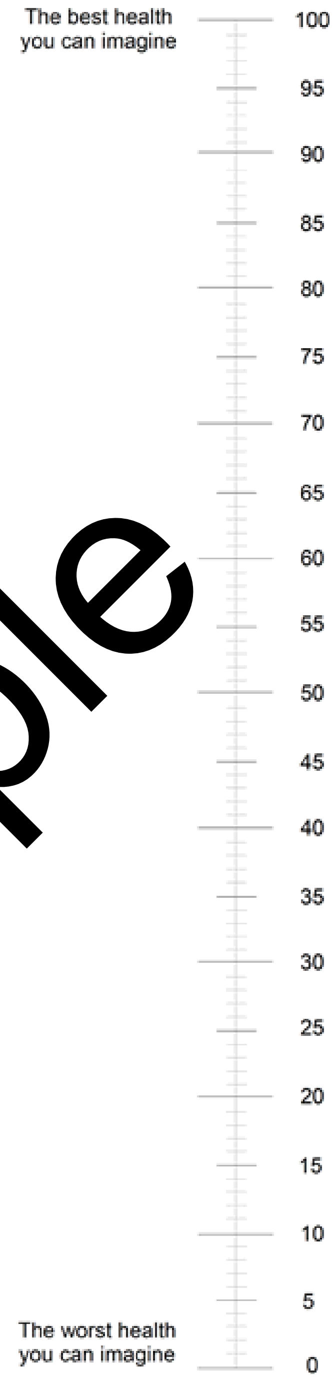
This scale is numbered from 0 to 100.

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.

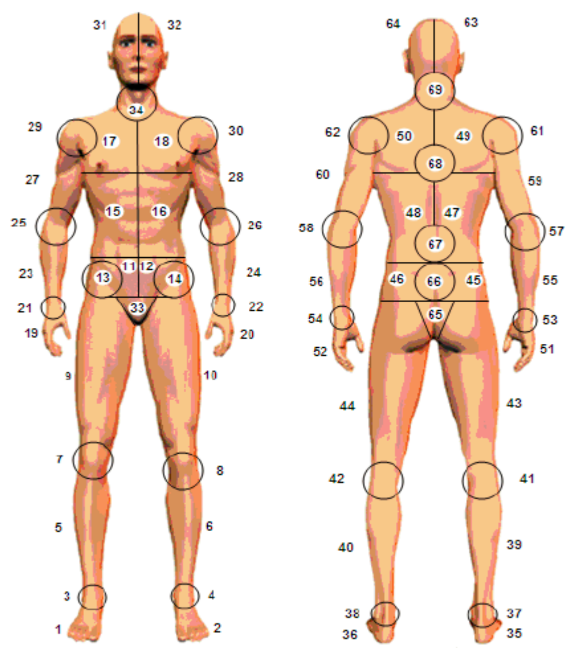


Health State: ___

Appendix 12. Pain DETECT Questionnaire

PAINDETECT QUESTIONNAIRE: (Page 1 of 2)

Please mark your **main area of pain**



Does your pain radiate to other regions of your body? yes ☐ no ☐

If yes, please draw the direction in which the pain radiates.

Continued to next page

PAINDETECT QUESTIONNAIRE: (Page 2 of 2)

How would you assess your pain **now**, at this moment?

0	1	2	3	4	5	6	7	8	9	10
none										max

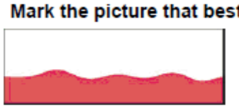
How strong was the **strongest** pain during the past 4 weeks?

0	1	2	3	4	5	6	7	8	9	10
none										max

How strong was the pain during the past 4 weeks **on average**?

0	1	2	3	4	5	6	7	8	9	10
none										max

Mark the picture that best describes the course of your pain.



Persistent pain with slight fluctuations ☐

Persistent pain with pain attacks ☐

Pain attacks without pain between them ☐

Pain attacks with pain between them ☐

Do you suffer from a burning sensation (e.g., stinging nettles) in the marked areas?
never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you have a tingling or prickling sensation in the area of your pain (like crawling ants or electrical tingling)?
never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Is light touching (clothing, a blanket) in this area painful?
never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you have sudden pain attacks in the area of your pain, like electric shocks?
never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Is cold or heat (bath water) in this area occasionally painful?
never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you suffer from a sensation of numbness in the areas that you marked?
never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Does slight pressure in this area, e.g., with a finger, trigger pain?
never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Appendix 13. Adjudication Categories

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

Appendix 14. Survey of Autonomic Symptoms

Table 1 Survey of Autonomic Symptoms*

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).

Appendix 15. Patient Reported Treatment Impact Assessment-modified (mPRTI)

PATIENT GLOBAL PREFERENCE ASSESSMENT

Before enrolling in this clinical trial, what treatment were you receiving for your low back pain?

Please Check (X) ONE only:

- ☐ (1) Injectable prescription medicines
- ☐ (2) Prescription medicines taken by mouth
- ☐ (3) Surgery
- ☐ (4) Prescription medicines and surgery
- ☐ (5) No treatment

Overall, do you prefer the drug that you received in this study to the treatment you received before this clinical trial?

Please Check (X) ONE only:

- ☐ (1) Yes, I definitely prefer the drug that I am receiving now
- ☐ (2) I have a slight preference for the drug that I am receiving now
- ☐ (3) I have no preference either way
- ☐ (4) I have a slight preference for my previous treatment
- ☐ (5) No, I definitely prefer my previous treatment

PATIENT WILLINGNESS TO USE DRUG AGAIN ASSESSMENT

In the future, would you be willing to use the same drug that you have received in this study for your low back pain?

- ☐ (1) Yes, I would definitely want to use the same drug again
- ☐ (2) I might want to use the same drug again
- ☐ (3) I am not sure
- ☐ (4) I might not want to use the same drug again
- ☐ (5) No, I definitely would not want to use the same drug again

Appendix 16. Treatment Satisfaction Questionnaire for Medication v.II

TREATMENT SATISFACTION QUESTIONNAIRE FOR MEDICATION - VERSION II TSQM:

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication over the last two to three weeks, or since you last used it. For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

- ☐ (1) Extremely Dissatisfied
- ☐ (2) Very Dissatisfied
- ☐ (3) Dissatisfied
- ☐ (4) Somewhat Satisfied
- ☐ (5) Satisfied
- ☐ (6) Very Satisfied
- ☐ (7) Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves symptoms?

- ☐ (1) Extremely Dissatisfied
- ☐ (2) Very Dissatisfied
- ☐ (3) Dissatisfied
- ☐ (4) Somewhat Satisfied
- ☐ (5) Satisfied
- ☐ (6) Very Satisfied
- ☐ (7) Extremely Satisfied

3. As a result of taking this medication, do you experience any side effects at all?

- ☐ (1) Yes
- ☐ (0) No

4. How dissatisfied are you by side effects that interfere with your physical health and ability to function (e.g., strength, energy levels)?

- ☐ (1) Extremely Dissatisfied
- ☐ (2) Very Dissatisfied
- ☐ (3) Somewhat Dissatisfied
- ☐ (4) Slightly Dissatisfied
- ☐ (5) Not at all Dissatisfied

TREATMENT SATISFACTION QUESTIONNAIRE FOR MEDICATION - VERSION II TSQM:

5. How dissatisfied are you by side effects that interfere with your mental function (e.g., ability to think clearly, stay awake)?
- ☐ (1) Extremely Dissatisfied
- ☐ (2) Very Dissatisfied
- ☐ (3) Somewhat Dissatisfied
- ☐ (4) Slightly Dissatisfied
- ☐ (5) Not at all Dissatisfied

6. How dissatisfied are you by side effects that interfere with your mood or emotions (e.g., anxiety/fear, sadness, irritation/anger)?
- ☐ (1) Extremely Dissatisfied
- ☐ (2) Very Dissatisfied
- ☐ (3) Somewhat Dissatisfied
- ☐ (4) Slightly Dissatisfied
- ☐ (5) Not at all Dissatisfied

7. How satisfied or dissatisfied are you with how easy the medication is to use?
- ☐ (1) Extremely Dissatisfied
- ☐ (2) Very Dissatisfied
- ☐ (3) Dissatisfied
- ☐ (4) Somewhat Satisfied
- ☐ (5) Satisfied
- ☐ (6) Very Satisfied
- ☐ (7) Extremely Satisfied

8. How satisfied or dissatisfied are you with how easy it is to plan when you will use the medication each time?
- ☐ (1) Extremely Dissatisfied
- ☐ (2) Very Dissatisfied
- ☐ (3) Dissatisfied
- ☐ (4) Somewhat Satisfied
- ☐ (5) Satisfied
- ☐ (6) Very Satisfied
- ☐ (7) Extremely Satisfied

TREATMENT SATISFACTION QUESTIONNAIRE FOR MEDICATION - VERSION II TSQM:

9. How satisfied or dissatisfied are you by how often you are expected to use/take the medication?
- ☐ (1) Extremely Dissatisfied
- ☐ (2) Very Dissatisfied
- ☐ (3) Dissatisfied
- ☐ (4) Somewhat Satisfied
- ☐ (5) Satisfied
- ☐ (6) Very Satisfied
- ☐ (7) Extremely Satisfied

10. How satisfied are you that the good things about this medication outweigh the bad things?
- ☐ (1) Extremely Dissatisfied
- ☐ (2) Very Dissatisfied
- ☐ (3) Dissatisfied
- ☐ (4) Somewhat Satisfied
- ☐ (5) Satisfied
- ☐ (6) Very Satisfied
- ☐ (7) Extremely Satisfied

11. Taking all things into account, how satisfied or dissatisfied are you with this medication?
- ☐ (1) Extremely Dissatisfied
- ☐ (2) Very Dissatisfied
- ☐ (3) Dissatisfied
- ☐ (4) Somewhat Satisfied
- ☐ (5) Satisfied
- ☐ (6) Very Satisfied
- ☐ (7) Extremely Satisfied

Appendix 17. France – Country specific administrative terms required for Contrat Unique

Good Clinical Practice training of investigators.

Prior to enrolment of any subjects, the investigator and any sub-investigators will complete the Pfizer-provided Good Clinical Practice training course ("Pfizer GCP Training") or training deemed equivalent by Pfizer. Any investigators who later join the Study will complete the Pfizer GCP Training or equivalent before performing Study-related duties. For studies of applicable duration, the investigator and sub-investigators will complete Pfizer GCP Training or equivalent every three years during the term of the Study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

Investigational product provision.

No subjects or third-party payers will be charged for investigational product.

Notification of the sponsor on regulatory inspection.

The investigator(s) will notify Pfizer or its service provider immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its service provider to prepare the study site for the inspection and will allow Pfizer or its service provider (if not prohibited by law) to be present during the inspection. The study site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its service provider. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its service provider with an opportunity to review and comment on responses to any such findings.

Appendix 18. Substudy- Follow up for Subjects Undergoing Total Joint Replacement of The Hip, Knee or Shoulder

SUBSTUDY SUMMARY

Measures to better characterize the joint safety issue have been developed and agreed with FDA. The post-arthroplasty data collected within this substudy, when aggregated with similar data from other tanezumab clinical studies, fulfills one component of the agreed risk characterization measures and is an attempt to address the potential concern that subjects treated with tanezumab have a different post-surgical outcome than those not treated with tanezumab. The total joint replacement data from completed tanezumab studies does not suggest a different post-surgical outcome in tanezumab treated subjects however those data were gathered retrospectively. The types of endpoints to be assessed in this prospective substudy and the duration of this substudy have been agreed to with the FDA. Every effort will be made to enroll all A4091059 subjects who undergo a qualifying total joint replacement into this substudy however it is acknowledged that to a certain extent the population enrolled in this substudy will be 'self-selected' and thus there maybe subjects with a qualifying total joint replacement who choose not to enter the substudy.

This substudy is a long-term observational study of subjects from tanezumab Study A4091059 (regardless of treatment group) who undergo a total knee, hip or shoulder replacement during participation in the study (treatment period or safety follow-up period). If while the subject is participating in this substudy, the subject undergoes an additional total joint replacement surgery or the site becomes aware that an additional total joint replacement surgery has been scheduled for the subject, the subject will be requested to provide information on the additional total joint replacement surgery as well. Finally, any subject with a qualifying total joint replacement after the last subject completes the treatment period in study A4091059 may be followed in Study A4091064.

This substudy is designed with a total duration of subject follow-up of 24 weeks after the total joint replacement surgery. There will be two methods of data collection utilized in this substudy: interview by site staff via the telephone and interactive web response system (IWRS) accessed by desktop, laptop or tablet computer (or paper if the subject has no access to the internet via a desktop, laptop or tablet computer). Following the surgery, the subject will be contacted monthly via telephone by study site personnel to ascertain whether the subject has experienced any adverse events and to record any concomitant analgesic medications the subject is taking as well as the reason for the medication use. An assessment of the subject’s overall satisfaction with his/her total joint replacement (IWRS), average pain in the replaced joint (IWRS), the subject’s level of function and activity in the replaced joint (IWRS) and physical rehabilitation activities (telephone interview) will be made at Weeks 4, 12 and 24. At Weeks 12 and 24, subjects will be queried during the telephone interview as to whether any additional or corrective procedures related to the total joint replacement are planned.

All events of total knee, hip or shoulder replacement will be reviewed by the Joint Safety Adjudication Committee (Adjudication Committee) established for the tanezumab clinical program. This Committee will adjudicate in an independent and blinded fashion if the event is primary osteonecrosis, worsening OA (further sub-divided into rapidly progressive OA (RPOA) type 1 or type 2, normal progression of OA or not enough information to distinguish between RPOA and normal progression of OA), subchondral insufficiency fracture, pathologic fracture, other (with diagnosis specified) or not enough information to specify a diagnosis. Prior to the Adjudication Committee's review of a given event, Committee members will be provided with blinded, available source documentation of progress reports from the investigator, orthopedic consult reports, operative reports, the pathology report from the central laboratory, radiology reports, Dual Energy X-ray Absorptiometry (DXA) reports, x-ray images and MRI for review. In addition, blinded summaries of the following data from Study A4091059 will be provided to the Committee members for review for each event undergoing adjudication: demographic and baseline characteristics, medical history and concomitant medications, study medication administration, non-drug treatments, subject disposition, efficacy data, adverse event information, neurological safety data and a serious adverse event narrative (if applicable).

Subjects, investigators, study coordinators, clinical site staff, orthopedic surgeons, and clinical research associates (CRAs), staff directly involved with this substudy at Pfizer and its designees will be blinded to treatment assignment in Study A4091059.

The number of subjects who will enroll in this substudy is unknown but is estimated to be less than 25 subjects. Also unknown is the distribution of subjects across treatment groups (ie, the treatment given in Study A4091059). Therefore, it is predicted that there will be insufficient statistical power to perform statistical inferential analyses. All analyses will be descriptive in nature. The data collected in this substudy will be combined with similar data collected in other tanezumab studies for further analysis. These aggregate analyses will be reported separately.

SUBSTUDY SCHEDULE OF ACTIVITIES

The Schedule of Activities table (Table 5) provides an overview of the substudy visits and procedures. Refer to the Procedures and Assessments sections of this appendix for detailed information on each procedure and assessment.

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

Table 5. SUBSTUDY SCHEDULE OF ACTIVITIES

Substudy Activities			**Post-Surgery**					
	Baseline[a]	**Day 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24/ET**
	Last visit in the A4091059 study[b] **or when notified of TJR surgery**	**Day of Surgery** (+10 days)	**Day 29** (±5 days)	**Day 57** (±5 days)	**Day 85** (±5 days)	**Day 113** (±5 days)	**Days 141** (±5 days)	**Day 169** (±5 days)
Pre-surgery Activities								
Informed Consent	X							
Inclusion Criteria Review	X							
Record ongoing adverse events and concomitant analgesic medication	X							
Train subject in the use of the interactive web response system (IWRS) if applicable[c]	X							
Assessment of Pain in Joint to be Replaced (11-point NRS) [d]	X							
Assessment of Functional Status (WOMAC [total hip or knee replacement candidates] or SPADI [total shoulder replacement candidates]) [d]	X							

Substudy Activities			Post-Surgery					
	Baseline[a]	**Day 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24/ET**
	Last visit in the A4091059 study[b] **or when notified of TJR surgery**	**Day of Surgery** (+10 days)	**Day 29** (±5 days)	**Day 57** (±5 days)	**Day 85** (±5 days)	**Day 113** (±5 days)	**Days 141** (±5 days)	**Day 169** (±5 days)
Provide surgery-related documents (Surgeon's Assessment of Procedural Difficulty and Pathology Specimen Collection/Shipment Guidelines to Surgeon	X							
Surgery - related Activities								
Obtain Surgeon's Assessment of Procedural Difficulty		X						
Confirm that pathologic specimens were shipped according to instructions		X						
Ensure required source documents are provided to Endpoint Management Team			X					
Post-Surgery Subject Follow-up Activities								
Telephone-based Assessments								
Adverse events			X	X	X	X	X	X
Concomitant analgesic medication use			X	X	X	X	X	X
Participation in physical rehabilitation activities related to the replaced joint			X		X			X
Additional or corrective procedures related to the replaced joint					X			X
Remind subjects not utilizing the IWRS to return paper-based assessments to the site within 5 days			X		X			X
Remind female subjects of contraceptive requirements (if applicable) [e]			X	X	X	X		

Substudy Activities			Post-Surgery					
	Baseline[a]	**Day 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24/ET**
	Last visit in the A4091059 study[b] or when notified of TJR surgery	**Day of Surgery** (+10 days)	**Day 29** (±5 days)	**Day 57** (±5 days)	**Day 85** (±5 days)	**Day 113** (±5 days)	**Days 141** (±5 days)	**Day 169** (±5 days)
Web-based Assessments [f]								
Subject's overall satisfaction with joint replacement surgery (SAPS)			X		X			X
Pain in replaced joint (11-point NRS)			X		X			X
Functional status (WOMAC [total hip and knee replacement subjects] or SPADI [total shoulder replacement subjects] [g]			X		X			X

a. Baseline activities must be conducted at the site.

b. Last visit in StudyA4091059 can be either the end of study visit or early termination visit.

c. Training in the use of the ePRO system ((IWRS) is appropriate for subjects who will have access to the internet via a desktop, laptop or tablet computer for the duration of the substudy.

d. To be collected via the Interactive Web Response System (IWRS). If the subject will not have access to the IWRS via a desktop, laptop or tablet computer for the duration of the substudy, paper versions of the assessment should be completed by the subject with subsequent entry into the IWRS by site staff. Note: the WOMAC and SPADI should be completed in their entirety.

e. Female subjects of child-bearing potential should be reminded of contraception requirements if less than 112 days (16 weeks) have elapsed since the last dose of subcutaneous study medication in Study A4091059.

f. If the subject does not have access to the IWRS via a desktop, laptop or tablet computer for the duration of the substudy, paper versions of the assessments should be completed by the subject. Completed paper assessments should be returned to the clinical site within 5 days of assessment completion. Site staff will enter the subject reported outcomes into the IWRS upon receipt of the completed assessment.

g. The WOMAC and SPADI should be completed in their entirety.

101. SUBSTUDY INTRODUCTION

Measures to better characterize the joint safety issue identified in 2010 have been developed and agreed with FDA. The post-arthroplasty data collected within this substudy, when aggregated with similar data from other tanezumab clinical studies, fulfills one component of the agreed risk characterization measures and is an attempt to address the potential concern that subjects treated with tanezumab have a different post-surgical outcome than those not treated with tanezumab. The total joint replacement data from completed tanezumab studies does not suggest a different post-surgical outcome in tanezumab treated subjects however those data were gathered retrospectively from previous studies. The types of endpoints to be assessed in this prospective substudy and the duration of the substudy have been agreed to with the FDA. Every effort will be made to enroll all Study A4091059 subjects who undergo a qualifying total joint replacement into this substudy however it is acknowledged that to a certain extent the population enrolled in this substudy will be 'self-selected' and thus there maybe subjects with a qualifying total joint replacement who choose not to enter the substudy.

101.1. Rationale for Selected Patient Reported Outcomes

Subject-based measures of health-related quality of life have increasingly been used by the orthopedic research community as a means to define a successful intervention.[a] Subject reported outcomes typically assessed post-arthroplasty include overall satisfaction with the joint replacement, pain and function.

The Self-Administered Patient Satisfaction Scale (SAPS) will be utilized to assess subject satisfaction with the joint replacement in this substudy. The SAPS is a multidimensional, disease specific measure that evaluates subject satisfaction with the outcome of hip or knee arthroplasty and was designed to be used in conjunction with other clinical measures and functional health status instruments to evaluate the results of hip and knee arthroplasty. The validity and reliability of the scale has been demonstrated.[b] The scale consists of four items focusing on satisfaction with the extent of pain relief, improvement in ability to perform home or yard work, ability to perform recreational activities and overall satisfaction with joint replacement.

Average pain in the joint to be replaced (pre-surgery) and the replaced joint (post-surgery) will be assessed with an 11-point Numeric Rating Scale (NRS) ranging from zero (no pain) to 10 (worst possible pain). The validity and reliability of the scale has been demonstrated.[c]

The functional measures chosen for this substudy were those which have been shown to be valid, reliable and sensitive and in addition were region-specific and easy to administer. Subjects undergoing total knee or hip replacement will be asked to complete the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) with the knee or hip that was replaced serving as the “index joint”. Subjects undergoing total shoulder replacement will be asked to complete the Shoulder Pain and Disability Index (SPADI).

The WOMAC is a self-administered condition-specific instrument which assesses pain, disability and joint stiffness in knee and hip osteoarthritis. It is a valid, reliable and responsive measure of outcome in subjects with arthritis and has been used extensively.[d,e,f]

The SPADI is a self-administered questionnaire that was developed to measure the pain and disability associated with shoulder pathology in people with shoulder pain of musculoskeletal, neurogenic or undetermined origin. The psychometric properties of the SPADI have been shown to be acceptable for research use and the SPADI has been recommended to assess outcomes in subjects undergoing shoulder arthroplasty.[g,h] The instrument consists of two dimensions (pain and function). The pain dimension consists of five questions regarding the severity of an individual's pain. Functional activities are assessed with eight questions designed to measure the degree of difficulty an individual has with various activities of daily living that require upper extremity use.

101.2. Interactive Web Response System

To avoid a social desirability bias in the subject reported outcomes, an Interactive Web Response System (IWRS) will be utilized in this substudy. Contingency plans will be in place to address system and/or connectivity issues with the IWRS.

However, eligibility for this substudy does not require access to the internet via a desktop, laptop or tablet computer so, for those subjects without access to the internet via a desktop, laptop or tablet computer, paper versions of the assessments will be utilized. Though not optimal, the use of two methods to collect subject reported outcomes will maximize the ability to capture information from all subjects who undergo a total knee, hip, or shoulder replacement surgery while participating in tanezumab StudyA4091059. Additional considerations which mitigate the concerns about using two methods to collect subject reported outcomes in the same substudy include that this substudy has not been formally powered and all analyses will be descriptive rather than inferential.

102. SUBSTUDY STUDY OBJECTIVE AND ENDPOINTS

102.1. Objective

- To describe the post-operative outcome of subjects who underwent a total knee, hip, or shoulder replacement while participating in tanezumab Study A4091059 (treatment period or safety follow-up period).

102.2. Endpoints

The following endpoints will be assessed in this substudy:

- Surgeon's Assessment of Procedural Difficulty: number and percentage of surgeries assessed as uneventful, minor complications or major complications.

- Subjects's overall satisfaction with surgery as assessed bythe Self-Administered Patient Satisfaction (SAPS) Scale: number and percentage of subjects satisfied vs unsatisfied with their total joint replacement at Week 24.

- Number and percentage of subjects with a post-surgical complication(s) up to Week 24 (derived from reported adverse events).

- Number and percentage of subjects with additional or corrective procedures related to their total joint replacement up to Week 24.

- Number and percentage of subjects participating in physical rehabilitation activities related to the replaced joint up to Week 24.

- Change from Baseline to Week 24 in average pain in the replaced joint.

- Change from Baseline to Week 24 in WOMAC Pain, Stiffness and Physical Function subscales in the replaced joint (subjects undergoing total hip or knee replacement surgery only).

- Change from Baseline to Week 24 in the SPADI in the replaced shoulder (subjects undergoing total shoulder replacement surgery only).

- Concomitant analgesic medication use.

103. SUBSTUDY STUDY DESIGN

This substudy is a long-term observational study of subjects from tanezumab Study A4091059 (regardless of treatment group) who undergo a total knee, hip or shoulder replacement during participation in the study (treatment period or safety follow-up period). If while the subject is participating in this substudy, the subject undergoes an additional total joint replacement surgery or the site becomes aware that an additional total joint replacement surgery has been scheduled for the subject, the subject will be requested to provide information on the additional total joint replacement surgery as well. Finally, any subject with a qualifying total joint replacement after the last subject completes the treatment period in study A4091059 may be followed in study A4091064.

This substudy is designed with a total duration of subject follow-up of 24 weeks after the total joint replacement surgery. There will be two methods of data collection utilized in this substudy: interview by site staff via the telephone and IWRS accessed by desktop, laptop or tablet computer (or paper if the subject has no access to the internet via a desktop, laptop or tablet computer). Following the surgery, the subject will be contacted monthly via telephone by study site personnel to ascertain whether the subject has experienced any adverse events and to record any concomitant analgesic medications the subject is taking as well as the reason for the medication use. An assessment of the subject's overall satisfaction with his/her total joint replacement (IWRS), average pain in the replaced joint (IWRS), the subject's level of function and activity in the replaced joint (IWRS) and physical rehabilitation activities (telephone interview) will be made at Weeks 4, 12 and 24. At Weeks 12 and 24, subjects will be queried during the telephone interview as to whether any additional or corrective procedures related to the total joint replacement are planned.

Any subject who expresses a desire to leave this substudy before 24 weeks of follow-up have been completed should be asked to complete all assessments scheduled for Week 24.

All events of total knee, hip or shoulder joint replacement will be reviewed by the Joint Safety Adjudication Committee (Adjudication Committee) established for the tanezumab clinical program. This Committee will adjudicate in an independent and blinded fashion if the event is primary osteonecrosis, worsening OA (further sub-divided into rapidly progressive OA (RPOA) type 1 or type 2, normal progression of OA or not enough information to distinguish between RPOA and normal progression of OA), subchondral insufficiency fracture, pathologic fracture, other (with diagnosis specified) or not enough information to specify a diagnosis. Prior to the Adjudication Committee's review of a given event, Committee members will be provided with blinded, available source documentation of progress reports from the investigator, orthopedic consult reports, operative reports, the pathology report from the central laboratory, radiology reports, DXA reports, x-ray images and MRI images for review. Sites will be requested to submit required source documentation to the Endpoint Management Team as soon as possible, and ideally within 29 ±5 days, after the total joint replacement surgery (ie, by the time the Week 4 visit occurs provided the source documentation has been completed). In addition, blinded summaries of the following data from Study A4091059 will be provided to the Committee members for review for each event undergoing adjudication: demographic and baseline characteristics, medical history and concomitant medications, study medication administration, non-drug treatments, subject disposition, efficacy data, adverse event information, neurological safety data and a serious adverse event narrative (if applicable).

The Adjudication Committee, in coordination with the Data Monitoring Committee (DMC), is responsible for ongoing analysis of these outcomes and for informing the sponsor of recommendations made.

Subjects, investigators, study coordinators, clinical site staff, orthopedic surgeons, clinical research associates (CRAs) staff directly involved with this substudy at Pfizer and its designees will be blinded to treatment assignment in Study A4091059. The data collected in this substudy will be combined with similar data collected in other tanezumab studies for analysis. Data analyses will be reported separately.

104. SUBSTUDY SUBJECT SELECTION

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

104.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team (ie, the investigator or a sub-investigator) before subjects are included in this substudy.

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

1. Evidence of a personally signed and dated informed consent document indicating the subject (or a legal representative) has been informed of all pertinent aspects of the substudy.

2. Subject has been randomized and treated with SC study medication in tanezumab Study A4091059 and has completed the study or has been withdrawn from the study.

3. Actual or planned total knee, hip or shoulder replacement surgery during tanezumab Study A4091059. Subjects undergoing total knee, hip or shoulder replacement surgery after the last subject completes the treatment period in Study A4091059 may be enrolled in Study A4091064 in order to complete the total joint replacement follow-up.

Note: additional procedures in a subject undergoing total joint replacement surgery (eg, revision of a previously replaced joint in addition to a new total joint replacement) will be allowed, but subjects undergoing solely sub-total arthroplastic procedures (eg, hemi-arthroplasty) will not be eligible.

4. Subject is willing and able to comply with scheduled visits and other substudy procedures.

104.2. Life Style Guidelines

All female subjects who, in the opinion of the investigator, are biologically capable of having children, and are sexually active, **who withdraw from Study A4091059 less than 16 weeks after the last dose of subcutaneous study medication** must agree to use two (2) methods of highly effective contraception **until 112 days (16 weeks) after the last dose of subcutaneous study medication**. Refer to Section 4.4 of the protocol for guidance on appropriate methods of contraception.

There are no contraception requirements for sexually active female subjects of childbearing potential who withdraw from Study A4091059 more than 16 weeks after the last dose of subcutaneous study medication.

104.3. Sponsor Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for this substudy is documented in the study contact list located in the Study Manual (see also Section 4.5 of the A4091059 protocol).

105. SUBSTUDY STUDY TREATMENTS

This is an observational study of subjects who were randomized and treated in tanezumab Study A4091059 and who subsequently underwent a total knee, hip or shoulder replacement during the treatment or safety follow up period. There are no study medications in this observational study.

Subjects, investigators, study coordinators, clinical site staff, orthopedic surgeons and clinical research associates (CRAs) and IWstaff directly involved with this substudy at Pfizer and its designees will be blinded to treatment assignment in Study A4091059.

105.1. Concomitant Medication(s)

No medications are specifically prohibited in this observational substudy.

Subjects who enter into this substudy <16 weeks after their last dose of subcutaneous study medication in Study A4091059 will be advised to avoid chronic non-steroidal anti-inflammatory drug (NSAID) use, until at least 16 weeks has elapsed, if possible.

Subjects will be instructed to keep a record of concomitant analgesic medication usage (including dose, dosing regimen and reason for use). This information will be recorded on the appropriate concomitant medication case report form (CRF) during the monthly telephone interviews.

106. SUBSTUDY STUDY PROCEDURES

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 this substudy. Such changes will be implemented administratively and documented in the appropriate venue (eg, site trial documentation and/or clinical study report).

Study visit windows are +10 days for activities related to the total joint replacement surgery and ±5 days for activities performed on Weeks 4, 8, 12, 16, 20 and 24. Site staff should make every effort to contact the subject within the defined visit window for Weeks 4, 8, 12, 16, 20 and 24 however, data obtained outside of the visit window while a deviation, should still be recorded. In the event that the activities related to a visit are performed within the extremes of the visit windows, following study visits and associated activities should be scheduled with reference to the total joint replacement surgery date. Subject scheduling issues should be brought to the attention of the study monitor for resolution.

The investigator must make sure that delegations of responsibility to site staff for administering the IWRS or entering data into the IWRS are specifically documented using the appropriate forms and are based on documented evidence of adequate training in administration and use of the IWRS. The investigator (or other site staff specifically delegated by the investigator) is responsible for regular monitoring of the compliance of the subjects with the required data entry by means of reports in the IWRS. The IWRS will also be programmed to notify designated site staff when data has not been recorded within the requested timeframe. Regardless of how the investigator delegates responsibility for administering the IWRS or entering data into the IWRS, the investigator remains responsible for providing adequate supervision and oversight of the investigator's colleagues, employees and any third parties as per FDA regulations and guidelines and Good Clinical Practice.

106.1. Baseline Visit

Baseline information for this substudy should be obtained as close as possible to, and prior to, the total joint replacement surgery. The Baseline Visit may coincide with the last visit in Study A4091059 (End of Study or Early Termination Visit) or occur when the site is notified of a planned total joint replacement surgery. Baseline Visit activities must be conducted at the clinical site.

Subjects should be queried about their access to the internet via a desktop, laptop or tablet computer so as to determine the appropriate format for the subject reported outcomes of pain in the joint to be (or post-surgery, that has been) replaced, functional status and, post-surgery, satisfaction with surgery.

Subjects with access to the internet via a desktop, laptop or tablet computer should be trained in the use of the IWRS and in their responsibilities for data entry in compliance with this substudy protocol. IWRS technical support (Help Desk) will be available to the subject for the duration of the study. Beginning with the Baseline Visit, subjects with access to the internet via a desktop, laptop or tablet computer should complete the aforementioned assessments via the IWRS. In the event of internet connectivity issues at the Baseline Visit, paper versions of the assessments should be completed.

Only subjects without access to the internet via a desktop, laptop or tablet computer during this substudy should complete the aforementioned assessments on paper for the duration of the substudy. Simple preference for the use of paper is not sufficient to allow its use by the subject who has access to the internet via a desktop, laptop or tablet computer during this substudy.

Except in unusual circumstances, subjects should not switch between paper-based and web-based completion of the subject reported outcome measures.

Thorough instruction should be provided for completion of self-administered scales (subject reported outcomes) however, no coaching or other interpretative assistance should be given to the subject during the completion of the questionnaires.

Telephone contact information should also be confirmed at the Baseline Visit.

106.1.1. Activities at the Baseline Visit

- Informed consent.
- Review of inclusion criteria.
- Record ongoing adverse events and concomitant analgesic medications.
- Assessment of pain in the joint to be replaced (11-point NRS).

- Assessment of functional status in the joint to be replaced (WOMAC for subjects undergoing total knee or hip replacement or SPADI for subjects undergoing total shoulder replacement). NOTE: the WOMAC and SPADI should be completed in their entirety.

- Subjects without access to the internet via a desktop, laptop or tablet computer should be provided with paper copies of the subject reported outcomes assessments. Subjects should be instructed on the timing of assessments and the need to return the assessments to the site as soon as possible, but no later than 5 days, after completion of the assessment. Site staff will enter the subject reported outcomes into the IWRS upon receipt of the completed assessment.

- Study site staff must contact the subject's orthopedic surgeon to discuss the completion of the required forms and specimen collection and handling. The surgeon will be provided with the surgery related documents (Surgeon's Assessment of Procedural Difficulty and instructions for the shipment of pathology specimens).

- If less than 112 days (16 weeks) have elapsed since the last dose of subcutaneous study medication in Study A4091059, female subjects of child-bearing potential should be reminded of contraceptive requirements.

106.2. Day of Surgery (+10 days)

During this interval, sites should ensure receipt of a completed Surgeon's Assessment of Procedural Difficulty and confirm that pathology specimens were shipped according to instructions. Required source document collection (eg, operative report and discharge summary) should begin in this interval.

Sites will be requested to submit required source documentation to the Endpoint Management Team as soon as possible, and ideally within 29 ±5 days, after the total joint replacement surgery (ie, by the time the Week 4 visit occurs provided the source documentation has been completed).

106.3. Week 4 (±5 days)

Site staff should contact the subject via telephone to:

- Query for adverse events.

- Query for concomitant analgesic medication use (record dose, dosing regimen and reason for use).

- Query about physical rehabilitation activities subsequent to the total joint replacement surgery.

During the telephone call, site staff should instruct the subject to complete the following assessments either via the IWRS or via paper, as established at the Baseline Visit:

- Pain in Replaced Joint (11-point NRS).
- Functional status (WOMAC for subjects with a total knee or hip replacement or SPADI for subjects with a total shoulder replacement); NOTE: the WOMAC and SPADI should be completed in their entirety.
- Overall satisfaction with joint replacement surgery measured by the Self-Administered Patient Satisfaction Scale (SAPS).

At the conclusion of the telephone call, site staff should:

- Remind subjects not utilizing the IWRS to return paper-based assessments to the site as soon as possible, but no later than 5 days, after completion of the assessment.
- If less than 112 days (16 weeks) have elapsed since the last dose of subcutaneous study medication in Study A4091059, remind female subjects of child-bearing potential of contraceptive requirements.
- Confirm the approximate timing of the next telephone call.

106.4. Week 8 (±5 days)

Site staff should contact the subject via telephone to:

- Query for adverse events.
- Query for concomitant analgesic medication use (record dose, dosing regimen and reason for use).

At the conclusion of the telephone call, site staff should:

- If less than 112 days (16 weeks) have elapsed since the last dose of subcutaneous study medication in Study A4091059, remind female subjects of child-bearing potential of contraceptive requirements.
- Confirm the approximate timing of the next telephone call.

106.5. Week 12 (±5 days)

Site staff should contact the subject via telephone to:

- Query for adverse events.
- Query for concomitant analgesic medication use (record dose, dosing regimen and reason for use).

- Query about physical rehabilitation activities subsequent to the total joint replacement surgery.

- Query for additional or corrective procedures related to the total joint replacement surgery.

During the telephone call, site staff should instruct the subject to complete the following assessments either via the IWRS or via paper, as established at the Baseline Visit:

- Pain in Replaced Joint (11-point NRS).

- Functional status (WOMAC for subjects with a total knee or hip replacement or SPADI for subjects with a total shoulder replacement); NOTE: the WOMAC and SPADI should be completed in their entirety.

- Overall satisfaction with joint replacement surgery measured by the SAPS.

At the conclusion of the telephone call, site staff should:

- Remind subjects not utilizing the IWRS to return paper-based assessments to the site as soon as possible, but no later than 5 days, after completion of the assessment.

- If less than 112 days (16 weeks) have elapsed since the last dose of subcutaneous study medication in Study A4091059, remind female subjects of child-bearing potential of contraceptive requirements.

- Confirm the approximate timing of the next telephone call.

106.6. Week 16 (±5 days)

Site staff should contact the subject via telephone to:

- Query for adverse events.

- Query for concomitant analgesic medication use (record dose, dosing regimen and reason for use).

At the conclusion of the telephone call, site staff should:

- If less than 112 days (16 weeks) have elapsed since the last dose of subcutaneous study medication in Study A4091059, remind female subjects of child-bearing potential of contraceptive requirements.

- Confirm the approximate timing of the next telephone call.

106.7. Week 20 (±5 days)

Site staff should contact the subject via telephone to:

- Query for adverse events.
- Query for concomitant analgesic medication use (record dose, dosing regimen and reason for use).

At the conclusion of the telephone call, site staff should:

- Confirm the approximate timing of the next telephone call.

106.8. Week 24 (±5 days)

Site staff should contact the subject via telephone to:

- Query for adverse events.
- Query for concomitant analgesic medication use (record dose, dosing regimen and reason for use).
- Query about physical rehabilitation activities subsequent to the total joint replacement surgery.
- Query for additional or corrective procedures related to the total joint replacement surgery.

During the telephone call, site staff should instruct the subject to complete the following assessments either via the IWRS or via paper, as established at the Baseline Visit:

- Pain in Replaced Joint (11-point NRS).
- Functional status (WOMAC for subjects with a total knee or hip replacement or SPADI for subjects with a total shoulder replacement); NOTE: the WOMAC and SPADI should be completed in their entirety.
- Overall satisfaction with joint replacement surgery measured by the SAPS.

At the conclusion of the telephone call, site staff should remind subjects not utilizing the IWRS to return paper-based assessments to the site as soon as possible, but no later than 5 days, after completion of the assessment.

106.9. Subject Withdrawal/Early Termination

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

If a subject cannot be contacted within the window for a scheduled visit, every effort should be made to contact the subject outside of the visit window. If a subject is thought to be lost to follow-up, the site must attempt to contact the subject with a minimum of 3 documented phone call attempts and, if phone calls are unsuccessful, a certified letter sent to the subject. All attempts to contact the subject and information received during the contact attempts must be documented in the subject's medical records. In any circumstance, every effort should be made to document the subject's outcome, if possible. The investigator should inquire about the reason for withdrawal, follow-up with the subject regarding any unresolved adverse events, query for any new adverse events, query about concomitant analgesic medication use, physical rehabilitation activities or corrective procedures related to the joint replacement surgery and request that the subject complete the following assessments via the IWRS tool or via paper, as established at the Baseline Visit:

- Pain in Replaced Joint (11-point NRS).
- Functional status (WOMAC for subjects with a total knee or hip replacement or SPADI for subjects with a total shoulder replacement) (WOMAC or SPADI).
- Overall satisfaction with joint replacement surgery measured by the SAPS.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

107. SUBSTUDY ASSESSMENTS

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

107.1. Surgeon's Assessment of Procedural Difficulty

Following the total joint replacement surgery, the orthopedic surgeon performing the surgery will be asked to answer the following question:

"Taking into consideration the subject's medical history and physical condition prior to surgery would you classify the operative procedure as:

1. Uneventful; or
2. Minor complications; or
3. Major complications

If the category of minor or major complications is chosen, the surgeon will be requested to specify the complication(s).

107.2. Pathology Specimens

Surgeons will be requested to ship pathology specimens from the total joint replacement surgery to a central laboratory for analysis. Detailed instructions for the shipping of pathology specimens will be provided. Identification of specimens of adequate quality, preparation and histopathologic examination of the specimens will be performed in a standardized manner by the central laboratory under the direction of an expert orthopedic pathologist. Pathology reports will generally be returned to the referring site within 7-10 days following completion of the report by the central laboratory.

107.3. Telephone-Based Assessments

Post-surgery, subjects will be contacted monthly via telephone by study site personnel.

107.3.1. Adverse Events

At each post-surgery telephone contact, subjects will be queried for the occurrence of adverse events. All adverse events reported by the subject must be recorded on the appropriate case report form (CRF).

A neurologic evaluation should be performed by a consulting neurologist if any of the following occurs:

- 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, pallanesthesia, paresthesia, peripheral sensory neuropathy, sciatica, sensory disturbance, sensory loss, 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 neurological adverse event which is non-neuropathic (eg, stroke, seizure) but which the investigator considers medically important should also result in a neurological consultation.

In these cases, a neurologic evaluation should be obtained as soon as possible after these signs and symptoms are known. The results of the neurological consultation will be recorded on the appropriate CRF. Adverse events will be reported where applicable as described in Section 8.

Subjects reporting adverse events with preferred terms of bradycardia, syncope, orthostatic hypotension (as defined in Section 7.3.5.1 of the A4091059 protocol), anhidrosis or hypohidrosis (any seriousness or severity) will be further evaluated for the presence of sympathetic autonomic neuropathy. Subjects will be referred for neurologic or cardiologic evaluation depending on symptom presentation and the investigator's assessment as to the specialist best able to evaluate the subject.

107.3.2. Concomitant Analgesic Medication

At each post-surgery telephone contact, subjects will be queried about concomitant analgesic medication usage including dose, dosing regimen and reason for use. This information should be recorded on the appropriate case report form (CRF).

107.3.3. Physical Rehabilitation Activities

At the Week 4, 12 and 24 post-surgery telephone contacts, subjects will be queried for physical rehabilitation activities related to the replaced joint. Specifically, subjects will be asked to respond yes or no to the following question:

- Are you participating in physical rehabilitation activities related to your replaced joint?

Subjects will be queried for details if the answer to the question is yes. This information should be recorded on the appropriate case report form (CRF).

107.3.4. Additional or Corrective Procedures

At the Week 12 and 24 post-surgery telephone contacts, subjects will be queried for additional or corrective procedures related to the total joint replacement surgery. Specifically, subjects will be asked to respond yes or no to the following question:

- Have you been told by your orthopedic surgeon that additional or corrective procedures (for example a revision or implant replacement) are necessary for your total joint replacement?

Subjects will be queried for details if the answer to the question is yes. If necessary, the orthopedic surgeon may be contacted to confirm/expand upon the information regarding additional or corrective procedures. This information should be recorded on the appropriate case report form (CRF).

107.4. Web-based Assessments

107.4.1. Overall Satisfaction with Joint Replacement Surgery

The Self-Administered Patient Satisfaction Scale (SAPS) evaluates subject satisfaction with the outcome of hip and knee arthroplasty and was designed to be used in conjunction with other clinical measures and functional health status instruments to evaluate the results of hip and knee arthroplasty.

The scale consists of four items focusing on satisfaction with the extent of pain relief, improvement in ability to perform home or yard work, ability to perform recreational activities and overall satisfaction with joint replacement.

Specifically, subjects will be asked to respond to the following questions:

- How satisfied are you with the results of your surgery?
- How satisfied are you with the results of your surgery for improving your pain?
- How satisfied are you with the results of surgery for improving your ability to do home or yard work?
- How satisfied are you with the results of surgery for improving your ability to do recreational activities?

Items are scored on a 4-point Likert scale with response categories consisting of 'very satisfied' (100 points), 'somewhat satisfied' (75 points), 'somewhat dissatisfied' (50 points), and 'very dissatisfied' (25 points). The scale score is the unweighted mean of the scores from the individual items, ranging from 25 to 100 per item with higher scores indicating greater satisfaction.

Subjects will be requested to complete the SAPS at Weeks 4, 12, and 24 either via the IWRS or by paper if the subject does not have access to the internet via a desktop, laptop or tablet computer. When completed on paper, the subject will be requested to return the assessment to the site as soon as possible, but no later than 5 days, after completion of the.

107.4.2. Pain in Replaced Joint

Average pain in the joint to be replaced (pre-surgery) and average pain in the replaced joint (post-surgery) will be assessed with an 11-point Numeric Rating Scale (NRS) ranging from zero (no pain) to 10 (worst possible pain).

<u>Question:</u>

Select the number that best describes your average pain in the (joint to be replaced or your replaced joint) the past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Possible Pain

At Baseline and at Weeks 4, 12 and 24 following total joint replacement surgery, subjects will be asked to indicate their average pain in the joint to be replaced (pre-surgery) or the replaced joint (post-surgery) via the IWRS or by paper if the subject does not have access to the internet via a desktop, laptop or tablet computer. When completed on paper, the subject will be requested to return the assessment to the as soon as possible, but no later than 5 days, after completion of the assessment.

107.4.3. Assessment of Functional Activity

Subjects undergoing total knee or hip replacement will be asked to complete the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) with the knee or hip that was replaced serving as the “index joint”. Subjects undergoing total shoulder replacement will be asked to complete the Shoulder Pain and Disability Index (SPADI). Descriptions of these assessments are provided below.

107.4.3.1. WOMAC

Subjects who will be proceeding to total knee or hip arthroplasty will be requested to complete all subscales of the WOMAC (ie, pain, physical function and stiffness) at Baseline and Weeks 4, 12, and 24 following total joint replacement surgery either via the IWRS or by paper if the subject does not have access to the internet via a desktop, laptop or tablet computer. When completed on paper, the subject will be requested to return the assessment to the site as soon as possible, but no later than 5 days, after completion of the assessment.

107.4.3.1.1. WOMAC Pain Subscale

The WOMAC Pain subscale is comprised of 5 questions regarding the amount of pain experienced due to OA in the index joint (selected study knee or hip) in the past 48 hours. **For this study, the index joint (selected study knee or hip) is defined as the joint to be or that has been replaced.** The WOMAC Pain subscale is calculated as the mean of the scores from the five individual questions, which may not be a whole (integer) number. The WOMAC Pain subscale NRS scores for each question, and the WOMAC Pain subscale score, range from 0 to 10, with higher scores indicating higher pain.

107.4.3.1.2. WOMAC Physical Function Subscale

The WOMAC Physical Function subscale is comprised of 17 questions regarding the degree of difficulty experienced due to arthritis in the index joint (selected study knee or hip) in the past 48 hours. **For this study, the index joint (selected study knee or hip) is defined as the joint to be or that has been replaced.** The WOMAC Physical Function subscale is calculated as the mean of the scores from the seventeen individual questions, which may not be a whole (integer) number. The WOMAC Physical Function subscale NRS scores for each question, and the WOMAC Physical Function subscale score, range from 0 to 10 with higher scores indicating worse function. This refers to the subject's ability to move around and perform usual activities of daily living.

107.4.3.1.3. WOMAC Stiffness Subscale

The WOMAC Stiffness subscale is comprised of 2 questions regarding the amount of stiffness experienced in the index joint (selected study knee or hip) in the past 48 hours. **For this study, the index joint (selected study knee or hip) is defined as the joint to be or that has been replaced.** The WOMAC Stiffness subscale is calculated as the mean of the scores from the two individual questions, which may not be a whole (integer) number. The WOMAC Stiffness subscale NRS scores for each question, and the WOMAC Stiffness subscale score, range from 0 to 10 with higher scores indicating more stiffness. Stiffness is defined as a sensation of decreased ease with which the subject moves the index knee or hip.

A copy of the WOMAC can be found in Appendix 19.

107.4.3.2. The Shoulder Pain and Disability Index (SPADI)

Subjects who will be proceeding to shoulder arthroplasty will be requested to complete both dimensions of the SPADI (ie, pain and function) at Baseline and Weeks 4, 12, and 24 following total joint replacement surgery either via the IWRS or by paper if the subject does not have access to the internet via a desktop, laptop or tablet computer. When completed on paper, the subject will be requested to return the assessment to the site as soon as possible, but no later than 5 days, after completion of the assessment.

The SPADI consists of two dimensions (pain and function). The pain dimension consists of five questions regarding the severity of an individual’s pain. Functional activities are assessed with eight questions designed to measure the degree of difficulty an individual has with various activities of daily living that require upper extremity use. The scores from both dimensions are averaged to derive a total score from 0 (best) to 100 (worst).

A copy of the SPADI can be found in Appendix 20.

108. SUBSTUDY ADVERSE EVENT REPORTING

Refer to Section 8 of the A4091059 protocol.

109. SUBSTUDY DATA ANALYSIS/STATISTICAL METHODS

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

109.1. Sample Size Determination

This substudy is designed to collect information sufficient to describe the post-operative outcome of subjects who underwent a total knee, hip, or shoulder replacement while participating in tanezumab Study A4091059. The number of subjects who will enroll in this substudy is unknown but is estimated to be less than 25 subjects. Also unknown is the distribution of subjects across treatment groups (ie, the treatment given in Study A4091059). Therefore, it is predicted that there will be insufficient statistical power to perform statistical inferential analyses. All analyses will be descriptive in nature. The data collected in this substudy will be combined with similar data collected in other tanezumab studies for further analysis. These aggregate analyses will be reported separately.

109.2. Analysis of Endpoints

Data from the substudy of subjects with total joint replacement of the knee, hip or shoulder will be presented at substudy Baseline or Day 1 (day of surgery) and each post-surgery visit using observed data (no imputation for missing data), and at Week 24 using Last Observation Carried Forward (LOCF) for missing data. Data will be shown at the timepoints specified and also using change from (pre-surgery) Baseline where relevant. Data will be shown overall, and split by treatment group.

For the Surgeon's Assessment of Procedural Difficulty, the number and percentage of subjects in each category (Uneventful, Minor complications, Major complications) will be presented. Complications reported by the surgeon will be listed.

For the Subject's Overall Satisfaction with Surgery assessments (using the Self-Administered Patient Satisfaction scale, SAPS), the responses [score] for each category (Very Satisfied [100], Somewhat Satisfied [75], Somewhat Dissatisfied [50], Very Dissatisfied [25]) will be summarized for each of the four items. The scale score is the unweighted mean of the scores from the individual items, ranging from 25 to 100 per item with higher scores indicating greater satisfaction. This total score will be summarized. Reponses to the question "How satisfied are you with the results of your surgery?" will also be summarized as satisfied (very satisfied and somewhat satisfied categories combined) and dissatisfied (somewhat dissatisfied and very dissatisfied categories combined).

Similarly, the number and percentage of subjects who have required (i) additional or corrective procedures related to their total joint replacement and (ii) participating in physical rehabilitation activities related to their replaced joint will be presented.

Average pain (NRS) in the replaced joint for all subjects, WOMAC Pain, Stiffness and Physical Function sub-scale scores for subjects who had total knee or hip replacement and SPADI Pain, function and total score for subjects who had total shoulder replacement will be summarized (including change from substudy Baseline summaries).

The number and percent of subjects with specified post-surgical complications will be presented. The list of post-surgical complications will be derived from reported adverse events and will consist of complications that are clinically significant and attributable to the total arthroplasty procedure eg, periprosthetic joint infection/wound infection, periprosthetic fracture, pulmonary embolism or sepsis/septicemia/shock. Literature reported analyses of post-surgical complications[i,j] will be used for guidance in developing the list of post-surgical complications. The list of post-surgical complications will be developed prior to database lock.

109.3. Data Monitoring Committee

Refer to Section 9.6 of the A4091059 protocol.

109.4. External Adjudication Committee

Refer to Section 9.5 of the A4091059 protocol.

110. SUBSTUDY QUALITY CONTROL AND QUALITY ASSURANCE

Refer to Section 10 of the A4091059 protocol.

111. SUBSTUDY DATA HANDLING AND RECORD KEEPING

Refer to Section 11 of the A4091059 protocol.

112. SUBSTUDY ETHICS

Refer to Section 12 of the A4091059 protocol.

113. SUBSTUDY DEFINITION OF END OF TRIAL

Refer to Section 13 of the A4091059 protocol.

114. SUBSTUDY SPONSOR DISCONTINUATION CRITERIA

Refer to Section 14 of the A4091059 protocol.

115. SUBSTUDY PUBLICATION OF STUDY RESULTS

Refer to Section 15 of the A4091059 protocol.

116. SUBSTUDY REFERENCES

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d. Rolfson O, et al. Use of patient-reported outcomes in the context of different levels of data. J Bone Joint Surg Am 2011; 93 Suppl3(E):66-71.

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h. Roy J-S, MacDermid JC and Woodhouse LJ. Measuring shoulder function: a systemic review of four questionnaires. Arthritis Care Res 2009; 61:623-632.

i. Grosso, LM et al., Hospital-Level Risk-Standardized Complication Rate Following Elective Primary Total Hip Arthroplasty and/or Total Knee Arthroplasty Measure Methodology Report 25 June 2012.

j. Bohsali KI, Wirth MA and Rockwood CA. Complications of total shoulder arthroplasty. J Bone Joint Surgery 88:2006; 2279 – 2292.

Appendix 19. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

WOMAC Osteoarthritis Index NRS3.1

CCI

[redacted]

WOMAC Osteoarthritis Index NRS3.1

CCI

[redacted]

WOMAC Osteoarthritis Index NRS3.1

CCI

[redacted]

WOMAC Osteoarthritis Index NRS3.1

CCI

[redacted]

WOMAC Osteoarthritis Index NRS3.1

CCI

[redacted]

WOMAC Osteoarthritis Index NRS3.1

CCI

[redacted]

Appendix 20. The Shoulder Pain and Disability Index (SPADI)

Shoulder Pain and Disability Index (SPADI)

Please place a mark on the line that best represents your experience during the last week attributable to your shoulder problem.

Pain scale

How severe is your pain?

Circle the number that best describes your pain where: 0 = no pain and 10 = the worst pain imaginable.

At its worst?	0	1	2	3	4	5	6	7	8	9	10
When lying on the involved side?	0	1	2	3	4	5	6	7	8	9	10
Reaching for something on a high shelf?	0	1	2	3	4	5	6	7	8	9	10
Touching the back of your neck?	0	1	2	3	4	5	6	7	8	9	10
Pushing with the involved arm?	0	1	2	3	4	5	6	7	8	9	10

Disability scale

How much difficulty do you have?

Circle the number that best describes your experience where: 0 = no difficulty and 10 = so difficult it requires help.

Washing your hair?	0	1	2	3	4	5	6	7	8	9	10
Washing your back?	0	1	2	3	4	5	6	7	8	9	10
Putting on an undershirt or jumper?	0	1	2	3	4	5	6	7	8	9	10
Putting on a shirt that buttons down the front?	0	1	2	3	4	5	6	7	8	9	10
Putting on your pants?	0	1	2	3	4	5	6	7	8	9	10
Placing an object on a high shelf?	0	1	2	3	4	5	6	7	8	9	10
Carrying a heavy object of 10 pounds (4.5 kilograms)	0	1	2	3	4	5	6	7	8	9	10
Removing something from your back pocket?	0	1	2	3	4	5	6	7	8	9	10