CLINICAL PROTOCOL

A PHASE 3 RANDOMIZED, DOUBLE-BLIND, ACTIVE-CONTROLLED, MULTICENTER STUDY OF THE LONG-TERM SAFETY AND EFFICACY OF SUBCUTANEOUS ADMINISTRATION OF TANEZUMAB IN JAPANESE ADULT SUBJECTS WITH CHRONIC LOW BACK PAIN

Compound:	PF-04383119
Compound Name:	Tanezumab
United States (US) Investigational New Drug (IND) Number:	NA
European Clinical Trials Database (EudraCT) Number:	NA
Protocol Number:	A4091063
Phase:	3

Document History

Document	Version Date	Summary of Changes
Amendment 2	14 September 2017	Considering study feasibility, number of subjects with 1-year exposure and capability of safety evaluation with the data from this study, the target sample size was changed to approximately 200 (170-220) subjects and Section 9.1 and associated texts throughout the protocol were updated. Additionally, it is acceptable to randomize more than 220 subjects from the safety perspective. Per change of target sample size, analysis of serum tanezumab and NGF levels at Weeks 2 and 4 were changed to be conducted for part of subjects (i.e. approximately 30% of subjects randomized at selected sites) to all subjects randomized. In order to clarify study procedure and description, administrative changes are added in Protocol Summary (Study Design), schedule of activities, Section 3 Study Design, Section 4.4 Life Style Guidelines and Section 5.6 Investigational Product Storage.
Amendment 1	02 August 2016	Inclusion criterion #6 and associated text throughout the protocol has been updated to expand the number of pre-study, non-steroidal anti-inflammatory drug (NSAID) chronic low back pain treatment regimens that are considered to be qualifying. The following pre-study NSAID treatment regimens are now considered to be qualifying for prospective study subjects: Loxoprofen 120 - 180 mg/day Meloxicam 5 - 15 mg/day Administrative updates in the Schedule of Activities and Sections 5.8.1.4, 6.7 and 7.4.4 to: • Provide flexibility in the allowance of

		screening stage 2. • Clarify that facet joint injections and nerve blocks are prohibited beginning 30 days prior to IPAP and through Week 64. • Correct the activity in telephone contacts at Weeks 68, 72 and 76. • Provide clarification of the intended follow-up for subjects with severe and persistent joint pain.
Original protocol	28 August 2015	N/A

Rationale for protocol amendment 2

Background

Although inclusion criterion #6 has been updated to expand the number of pre-study non-steroidal anti-inflammatory drug (NSAID) for chronic low back pain treatment regimens that are considered to be qualifying in the amendment 1 (version date: 2 August 2016), an expected effect of enhancement of patient enrolment has not been achieved. Considering study feasibility, number of subjects with 1-year exposure and capability of safety evaluation with the data from this study, the protocol was amended to revise the target sample size.

Amendment 2

Considering study feasibility, number of subjects with 1-year exposure and capability of safety evaluation with the data from this study, the target sample size was updated to approximately 200 (170-220) subjects. However, it is acceptable to randomize more than 220 subjects from the safety perspective because primary objective is to evaluate the long-term safety.

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 (CLBP).

This study will investigate the long term safety and efficacy 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 evaluate the long-term safety of tanezumab 5 mg and 10 mg administrated SC every 8 weeks (7 administrations). In addition, the study will evaluate the long-term analgesic efficacy of tanezumab 5 mg and 10 mg SC administered every 8 weeks (7 administrations).

STUDY OBJECTIVES AND ENDPOINTS

Primary Objective:

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

Secondary Objective:

- Demonstrate the long-term analgesic efficacy of tanezumab 10 mg and 5 mg SC administered every 8 weeks (7 administrations).

Primary Endpoints:

Safety Measures

- Adverse events.
- Standard safety assessments (safety laboratory testing [chemistry and hematology], vital signs).
- Orthostatic (supine/standing) blood pressure assessments.
- Survey of Autonomic Symptoms (SAS) 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.

Secondary Endpoints:

Efficacy-Related Endpoints

- Change from Baseline to Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, 56 and 64 in average Low Back Pain Intensity (LBPI) score as measured by an 11-point Numeric Rating Scale (NRS).
- Change from Baseline to Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56 and 64 in the Roland-Morris Disability Questionnaire (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.
- Response as defined by a ≥30%, ≥50%, ≥70% and a ≥90% reduction from Baseline in weekly average LBPI score derived from the subject diary at Weeks 16, 24, 40 and 56.
- Change from Baseline to Weeks 2, 4, 8, 16, 24, 40, 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 16, 24, 40 and 56.
- Treatment Response: Improvement of ≥2 points in Patient's Global Assessment of Low Back Pain at Weeks 16, 24, 40 and 56.
- Euro Quality of Life Health State Profile (EQ-5D-5L™) dimensions and overall health utility score at Baseline, Weeks 16 and 56.
- Work Productivity and Activity Impairment Questionnaire: Low Back Pain (WPAI:LBP) change from Baseline to Week 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 64.
- Usage of rescue medication (amount taken) during Weeks 2, 4, 8, 12, and 16.
- Health Care Resource Utilization (HCRU) 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.

Tertiary Endpoints

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

STUDY DESIGN

This is a randomized, double-blind, active-controlled, multicenter, parallel-group Phase 3 study of the safety and efficacy of tanezumab when administered by SC injection for up to 56 weeks in subjects with chronic low back pain. Subjects will be randomized to 1 of 3 treatment groups in a 1:1:1 ratio. Treatment groups will include:

1. Placebo SC matching tanezumab administered at an 8-week interval (total of 7 times) plus celecoxib 100 mg twice a day (BID) to be administered orally for 56 weeks.
2. Tanezumab 5 mg SC administered at an 8-week interval (total of 7 times) plus placebo matching celecoxib to be administered orally BID for 56 weeks.
3. Tanezumab 10 mg SC administered at an 8-week interval (total of 7 times) plus placebo matching celecoxib to be administered orally BID for 56 weeks.

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), Double-blind Treatment (56 weeks) and Follow-up (24 weeks).

STATISTICAL METHOD

In terms of study feasibility and safety evaluation, the total sample size will be approximately 200 subjects (170-220 subjects, approximately 66 subjects [56-73 subjects] per treatment group). However, it is acceptable to randomize more than 220 subjects from the safety perspective as described below because primary objective is to evaluate the long-term safety.

Japanese CLBP subjects are enrolled in two studies (A4091059 and this study). In ongoing A4091059 study (randomization was finished in June 2017), 129 Japanese subjects were randomized and approximately 57 Japanese CLBP subjects are expected to be initially randomized to the tanezumab arm. Considering approximately 133 (113-146) subjects are expected to be randomized to the tanezumab arm in this study, the safety data will be collected from approximately 190 (170-203) Japanese CLBP subjects treated with tanezumab.

The proportion of subjects expected to complete this study was calculated as approximately 54% based on two OA phase 3 studies (A4091011, A4091014) and approximately 34% based on one CLBP phase 3 study (A4091012), and therefore the proportion of completers of this study is estimated to be between 34% and 54%. If the proportion of completers is at least 43% in CLBP program, approaching 100 subjects would be treated with tanezumab for a minimum of one year.

As described below, when approximately 200 (170-220) Japanese subjects are enrolled in this study, the adverse events related to abnormal peripheral sensation and decreased sympathetic function are expected to occur in several Japanese subjects, so neurological safety can be evaluated with high probability in Japanese subjects.

Assuming that the true incidence of adverse events related to abnormal peripheral sensation in CLBP subjects enrolled in A4091059 and this study is 10%, when 170 subjects are enrolled in this study (approximately 113 subjects will be treated with tanezumab), these adverse events are expected to occur in 7 to 15 subjects (6%-13%) in this study at a probability of ≥80%, and in 12 to 22 subjects (7%-13%) in combined A4091059 and this study (approximately 170 subjects will be treated with tanezumab) at a probability of ≥80%.

Assuming that the true incidence of adverse events related to decreased sympathetic function in CLBP subjects enrolled in A4091059 and this study is 6%, when 170 subjects are enrolled in this study, these adverse events are expected to occur in 4 to 10 subjects (4%-9%) in this study at a probability of ≥80%, and in 6 to 14 subjects (4%-8%) in combined A4091059 and this study at a probability of ≥80%.

Main Safety and Efficacy Analysis

The efficacy and safety population will be the ITT population, defined as all randomized subjects who received SC investigational product (either tanezumab or matching placebo).

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.

The incidence of subjects with any of the 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 subject years of exposure (treatment plus follow-up periods), for individual treatment groups and differences between tanezumab treatment groups and the celecoxib treatment group. The risk ratio and risk difference with 95% confidence intervals will be calculated for the comparisons of each tanezumab group versus the celecoxib group.

For the efficacy endpoints, summary statistics will be shown by timepoints and by treatment group. For the continuous endpoints and the binary endpoints, the difference with 95% confidence intervals between tanezumab treatment groups and the celecoxib treatment group will be calculated, but no inferential testing will be performed.

DATA MONITORING COMMITTEE

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

SCHEDULE OF ACTIVITIES

The Schedule of Activities tables provide 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 well-being of the subject.

Table 1. Schedule of Activities: Screening through Week 56

	Screen			Treatment Period									
Visit Indentifiers	**SC. Stage 1**	**SC. Stage 2**	**IPAP**	**Baseline[a]**	**Week 2**	**Week 4**	**Week 8[a]**	**Week 12[b]**	**Week 16[a]**	**Week 24[a]**	**Weeks 32, 40, 48[a]**	**Weeks 20, 28, 36, 44, 52[b]**	**Week 56/ End of Treatment**
Study Activities	**Day - 37 to -5**		**Day-5 to -1**	**Day 1 Dosing Visit**	**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												
Height/BMI/ Smoking Status/Female Hormonal Status/Alcohol Use	X												
Body Weight	X												X

	Screen			Treatment Period									
Visit Indentifiers	**SC. Stage 1**	**SC. Stage 2**	**IPAP**	**Baseline[a]**	**Week 2**	**Week 4**	**Week 8[a]**	**Week 12[b]**	**Week 16[a]**	**Week 24[a]**	**Weeks 32, 40, 48[a]**	**Weeks 20, 28, 36, 44, 52[b]**	**Week 56/ End of Treatment**
Study Activities	**Day - 37 to -5**		**Day-5 to -1**	**Day 1 Dosing Visit**	**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)**
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)[c]	X			X	X	X	X		X	X	X		X
Adverse event assessment				X	X	X	X	X	X	X	X	X	X
Review weekly joint pain scores				X	X	X	X	X	X	X	X	X	X
Concomitant medication review				X	X	X	X	X	X	X	X	X	X
Washout of prohibited Pain Medications (Prior to Day -5)	→												
Subject Reported Assessments Completed at Study Visits (collected via tablet device at site)													
BPI-sf				X	X	X	X		X	X	X[d]		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

	Screen			Treatment Period									
Visit Indentifiers	**SC. Stage 1**	**SC. Stage 2**	**IPAP**	**Baseline[a]**	**Week 2**	**Week 4**	**Week 8[a]**	**Week 12[b]**	**Week 16[a]**	**Week 24[a]**	**Weeks 32, 40, 48[a]**	**Weeks 20, 28, 36, 44, 52[b]**	**Week 56/ End of Treatment**
Study Activities	**Day - 37 to -5**		**Day-5 to -1**	**Day 1 Dosing Visit**	**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)**
Health Care Resource Utilization (HCRU)				X									
TSQM									X				X
mPRTI									X				X
Survey of Autonomic Symptoms (SAS)	X									X			X
Subject Daily and Weekly Assessments (IRT)													
LBPI score[e]	X[f]		X[f]	---------- (Weekly via IRT [handheld device]) ----------									
Rescue medication usage[e]		---------- (Daily via IRT [handheld device]) ----------								--- (Weekly via IRT [handheld device]) ---			
Record joint pain, if applicable[g]	X	---------- (Weekly via IRT [handheld device]) ----------											
Concomitant NSAID (outside of oral investigational product) usage		---------- (Weekly via IRT [handheld device]) ----------											
Radiographic Assessments													
X-rays of the hips, knees and shoulders	X									X[h]			X
Central reader to confirm radiologic eligibility	X									X[h]			
Compliance assessments													
Assess compliance with oral investigational product (Celecoxib or placebo matching for Celecoxib)					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
Rescue medication compliance				X	X	X	X	X	X	X	X	X	X

	Screen			Treatment Period									
Visit Indentifiers	**SC. Stage 1**	**SC. Stage 2**	**IPAP**	**Baseline[a]**	**Week 2**	**Week 4**	**Week 8[a]**	**Week 12[b]**	**Week 16[a]**	**Week 24[a]**	**Weeks 32, 40, 48[a]**	**Weeks 20, 28, 36, 44, 52[b]**	**Week 56/ End of Treatment**
Study Activities	**Day - 37 to -5**		**Day-5 to -1**	**Day 1 Dosing Visit**	**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)**
NSAID (outside of oral investigational product) limit compliance					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
Laboratory													
Hepatitis Screen (Hepatitis B & C); HIV, Urine Toxicology screen	X												
Hemoglobin A1c	X												
Serum FSH testing[i]	X												
Serum/Urine Pregnancy Test[j]	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[k]				X	X	X	X		X		X[l]		X
Serum Pharmacodynamic sample (NGF)[k]				X	X	X	X				X[l]		X
Serum Anti-Drug Antibody[k]				X			X		X		X[l]		X
Serum and urine biomarkers[m]				X									
Banked biospecimen (whole blood)				X									

	Screen			Treatment Period									
Visit Indentifiers	**SC. Stage 1**	**SC. Stage 2**	**IPAP**	**Baseline[a]**	**Week 2**	**Week 4**	**Week 8[a]**	**Week 12[b]**	**Week 16[a]**	**Week 24[a]**	**Weeks 32, 40, 48[a]**	**Weeks 20, 28, 36, 44, 52[b]**	**Week 56/ End of Treatment**
Study Activities	**Day - 37 to -5**		**Day-5 to -1**	**Day 1 Dosing Visit**	**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)**
Trial Treatment													
Pre-study Celecoxib Dispensed/Regimen Stabilization	X	At least 2 or 3 weeks prior to Baseline (Day 1) visit[n]											
Assess treatment response and eligibility to continue in the trial[o]									X[o]				
Randomization				X									
SC investigational product[p]				X			X		X	X	X		
Blinded Celecoxib (Oral investigational product)				----------X----------									
Dispense Blinded Celecoxib (Oral investigational product)				X	X	X	X		X	X	X		
Dispense rescue medication	X			X	X	X	X		X	X	X		X

Table 2. Schedule of Activities: Follow-up Period

	Follow-up Period				Early Termination (ET) Procedure				
Visit Indentifiers	**Week 60**	**Week 64**	**Week 68, 72, 76**	**Week 80 End of Study**	**ET Visit 1**	**ET Telephone Contact 1**	**ET Visit 2**	**ET Telephone Contact 2**	**ET Visit 3**
Study Activities	**(±7 days) Telephone Contact**	**Day 449 (±7 days)**	**(±7 days) Telephone 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
Electrocardiogram (12-lead)				X	X				X
Body weight					X				
General Physical Examination					X				
Musculoskeletal Physical Examination		X		X	X		X		X
Neurologic Exam/Neuropathy Impairment Score (NIS)[c]		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
Subject Reported Assessments Completed at Study Visits (collected via tablet device at site)									
BPI-sf		X			X		X		
RMDQ		X			X		X		
Patient Global Assessment of Low Back Pain		X			X		X		
WPAI:LBP		X			X		X		
EQ-5D-5L					X				
HCRU		X		X			X		X
TSQM					X				
mPRTI					X				
Survey of Autonomic Symptoms (SAS)				X	X				X

	Follow-up Period				Early Termination (ET) Procedure				
Visit Indentifiers	**Week 60**	**Week 64**	**Week 68, 72, 76**	**Week 80 End of Study**	**ET Visit 1**	**ET Telephone Contact 1**	**ET Visit 2**	**ET Telephone Contact 2**	**ET Visit 3**
Study Activities	**(±7 days) Telephone Contact**	**Day 449 (±7 days)**	**(±7 days) Telephone 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)**
Subject Weekly Assessments (IRT)									
LBPI score[e]	---------- X ----------				---------- X ----------				
Rescue medication use[e]	---------- X ----------				---------- X ----------				
Record joint pain, if applicable[g]	---------- X ----------				---------- X ----------				
Concomitant NSAID (outside of oral investigational product) usage	---------- X ----------				---------- X ----------				
Radiographic Assessments									
X-rays of the hips, knees and shoulders				X	X				X
Compliance assessments									
Compliance with weekly diary entries via IRT	X	X	X		X	X	X	X	
Rescue medication compliance	X	X			X	X	X		
NSAID (outside of oral investigational product) limit compliance	X	X			X	X	X		
Remind subject of contraceptive requirements	X	X			X	X	X		
Laboratory									
Serum/Urine Pregnancy Test[j]		X			X		X		
Hematology		X					X		
Blood Chemistry		X					X		
Serum/Plasma Retention Sample		X			X		X		
Plasma Pharmacokinetic sample[k]		X			X		X		
Serum Pharmacodynamic sample (NGF)[k]		X			X		X		
Serum Anti-Drug Antibody[k]		X		X	X		X		X

	Follow-up Period				Early Termination (ET) Procedure				
Visit Indentifiers	**Week 60**	**Week 64**	**Week 68, 72, 76**	**Week 80 End of Study**	**ET Visit 1**	**ET Telephone Contact 1**	**ET Visit 2**	**ET Telephone Contact 2**	**ET Visit 3**
Study Activities	**(±7 days) Telephone Contact**	**Day 449 (±7 days)**	**(±7 days) Telephone 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)**
Trial Treatment									
Dispense rescue medication		X			X		X		
Assign standard of care treatment as needed		X					X		

Abbreviations: → = Ongoing/Continuous event; BMI = body mass index; BP = Blood Pressure; BPI-sf = Brief Pain Inventory-Short Form, ECG = Electrocardiogram; EQ-5D-5L = EuroQol 5 Dimension ; FSH = Follicle Stimulating Hormone; HCRU = Health Care Resource Utilization; HIV = Human Immunodeficiency Virus; HR = Heart Rate; IPAP = Initial Pain Assessment Priod; IRT = Interactive Response Technology; LBPI = Low Back Pain Intensity; mPRTI = Patient Reported Treatment Impact assessment-modified; NGF = Nerve Growth Factor; NIS = Neuropathy Impairment Score; NSAID = Non-Steroidal Anti-Inflammatory Drug; PD = Pharmacodynamics; PK = Pharmakokinetic; RMDQ = Roland-Morris Disability Questionnaire; SAS = Survey of Autonomic Symptoms; SC = Subcutaneous; SC. = Screening; TSQM (v.II) = Treatment Satisfaction Questionnaire Medicine version II; WPAI:LBP = Work Productivity and Activity Impairment Questionnaire: Low Back Pain

a. All study activities at Baseline (Day 1), Weeks 8, 16, 24, 32, 40 and 48 should be performed prior to dosing with investigational product, unless otherwise noted.

b. Telephone Contact Visit: Contact subject and review adverse events (including any new or persistent joint pain, joint procedures or surgeries), compliance with contraceptive requirements, concomitant medications and concomitant use of analgesics for chronic low back pain, as appropriate. 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.

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

d. BPI-sf to be conducted at Week 40 only.

e. LBPI scores will be collected daily during the Intial Pain Assessment Period (IPAP) and weekly from Baseline through to Week 64 using IRT. Rescue medication use will be collected daily up to Week 16 and weekly from Week 16 to 64 via IRT.

f. At the Screening stage 1 visit only, in order to determine eligibility, the LBPI score will be collected via the IRT. During the IPAP (within a 5 day consecutive period prior to Baseline), the subjects will record their daily LBPI score use by the IRT.

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

h. At Week 24, sites must receive confirmation of continued radiologic eligibility from the Central Reader prior to administering the Week 24 SC investigational product. Refer to Section 6.4.7.

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

j. 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 6.9). 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.

k. On dosing visits, samples for ADA should be obtained pre-dose at Baseline and Weeks 8, 16, 32 and 48, and at Weeks 56, 64 and 80, or at early termination. Samples for PK should be obtained pre-dose at Baseline and Weeks 8, 16, 32 and 48, and at Weeks 2, 4, 56 and 64, or early termination. samples for NGF should be obtained pre-dose at Baseline and Weeks 8, 48, and at Weeks 2, 4, 56 and 64, or early termination.

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

m. 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.

n. Pre-study NSAID (Celecoxib) will be dispensed in the Screening period and subjects will be reqired to maintain 70% (5 of 7 days per week) compliance during the final two weeks (subjects who were receiving celecoxib as pre-study treatment) or three weeks (subjects who were receiving loxoprofen or meloxicam as pre-study treatment) of the Screening period immediately prior to Baseline (Day1) (refer to Section 6.1.2 for additional detail regarding Celecoxib regimen stabilization).

o. At the Week 16 visit, all subjects must have at least a 30% reduction in weekly average LBPI score relative to Baseline and at least a 15% reduction in weekly average LBPI score from Baseline at any week from Week 1 to Week 15 in order to continue order to continue investigational product. Subjects who do not meet these response criteria will be discontinued from the Treatment Period and enter Early Termination Follow-up Period.

p. 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 investigational product.

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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 and modulation of the pain response.[1,2] Many non-clinical 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.[2,3] Together these observations suggest that NGF may play a role in pain secondary to inflammation or injury.

1.2.2. Description of Investigational Product

Tanezumab is a humanized immunoglobulin G Type 2 (IgG_2) monoclonal antibody, derived from a murine precursor with a mutation in the Fc portion of the antibody to decrease its ability to activate complement or to support antibody dependent cell-mediated cytotoxicity.[4,5] Tanezumab is highly potent in sequestering NGF and preventing interaction with the trkA or p75 receptors.

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.[6] 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%[7] and a recent survey in 2008 estimated the prevalence of chronic low back pain to be 8.1%.[8] 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.[9] In Japan, a large population-based survey found that 3.87% of the population had experienced chronic, disabling low back pain during their lifetime.[10]

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.[11] 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.[11] 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. Most of these studies were conducted in subjects with osteoarthritis of the knee or hip. 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. 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;[12] 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;[13] 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;[14] 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.

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).[13]

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.

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.

Further efficacy and safety results from chronic low back pain studies with tanezumab are described in the tanezumab Investigator's Brochure.

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

Table 3. 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 based on the results of study A4091027 which compared SC versus IV administration in subjects with osteoarthritis. The incidence of adverse events, withdrawals due to adverse events, and serious adverse events in subjects treated with tanezumab monotherapy (5-10 mg) was similar to subjects receiving active comparator treatment and increased over placebo-treated subjects. 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 patients 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).[14,15,16] 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.

1.2.4.5. Joint Safety

A comprehensive investigation and analyses related to joint-safety has been 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.[17]

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 (ACR) 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 investigational product 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.

1.2.4.6. Experience in Japanese Subjects

1.2.4.6.1. Study A4091013 in Healthy Volunteers

Study A4091013[18] was an absolute bioavailability study in which a total of 76 subjects, including 17 Japanese subjects, received tanezumab either intravenously or subcutaneously via a single injection in the abdomen. Dose levels were 10 mg IV (n=19), 5 mg SC (n=20), 10 mg SC (n=19) or 19 mg SC (n=18). Based on geometric mean C_{max} values, peak exposure for the 10 mg IV treatment was more than 3-fold higher than that for the 10 mg SC treatment. However, comparison of median concentrations for the 10 mg doses shows that after approximately 4 weeks, tanezumab exposure was comparable between the IV and SC routes for the remaining 12 weeks of the study. Terminal half-life was comparable after IV and SC administration in the range of 17 to 24 days. Following IV administration of tanezumab, median T_{max} for the combined Japanese and non-Japanese population was 0.17 hours, corresponding to the first postdose sample (10 minutes after the start of the 1 minute IV push). Subcutaneous absorption of tanezumab into the systemic circulation was relatively slow, with median T_{max} values of 10 to 12 days for the combined population following SC administration. Comparison of geometric mean C_{max} and AUC_{inf} values after SC administration suggests exposure increased proportionally with increasing dose across the dose levels tested. Based on the observed dose linearity, data for all 3 SC treatments were combined for the statistical assessment of absolute bioavailability. The ratio (90% CI) of adjusted geometric means for SC versus IV AUC_{inf} was 68.27% (62.05%, 75.11%), indicating an absolute bioavailability of 68% for the SC treatments in this study.

1.2.4.6.2. Study A4091022 in Osteoarthritis Subjects

A total of 83 Japanese subjects were enrolled in Study A4091022[19], a study designed to examine the safety and efficacy of tanezumab in Japanese subjects with osteoarthritis of the knee. In part 1 of the study, 42 subjects were randomized to receive a single IV dose of tanezumab or placebo. Subjects randomized to tanezumab received one of five possible doses (10 µg/kg, 25 µg/kg, 50 µg/kg, 100 µg/kg or 200 µg/kg). Assuming a 100 kg subject, these tanezumab doses represent fixed doses of approximately 1 mg, 2.5 mg, 5 mg, 10 mg and 20 mg, respectively. In part 2 of the study, 41 other subjects were randomized to receive a single IV dose of tanezumab or placebo. Subjects randomized to tanezumab received one of four possible doses (10 µg/kg, 25 µg/kg, 50 µg/kg, or 100 µg/kg). In total, 67 subjects received a single dose of tanezumab and 16 received placebo.

Tanezumab PK were evaluated over the 16 week duration of the study after administration of a single IV dose of tanezumab at either 10 µg/kg (n=6), 25 µg/kg (n=4), 50 µg/kg (n=5), 100 µg/kg (n=5), or 200 µg/kg (n=6). Systemic exposure of tanezumab generally appeared to increase dose-proportionally across the dose range studied. Plasma tanezumab concentrations declined over time with an apparent mean elimination half-life of approximately 12.5 to 23.5 days. The geometric mean clearance of tanezumab from plasma ranged from 2.55 to 3.84 mL/kg/day across dose levels. The geometric mean V_{ss} ranged from 50.0 to 82.6 mL/kg. In addition, after a single IV administration of tanezumab the geometric mean C_{max} were 309, 682, 1050, 2400, and 4790 ng/mL for doses 10, 25, 50, 100, and 200 µg/kg, respectively.

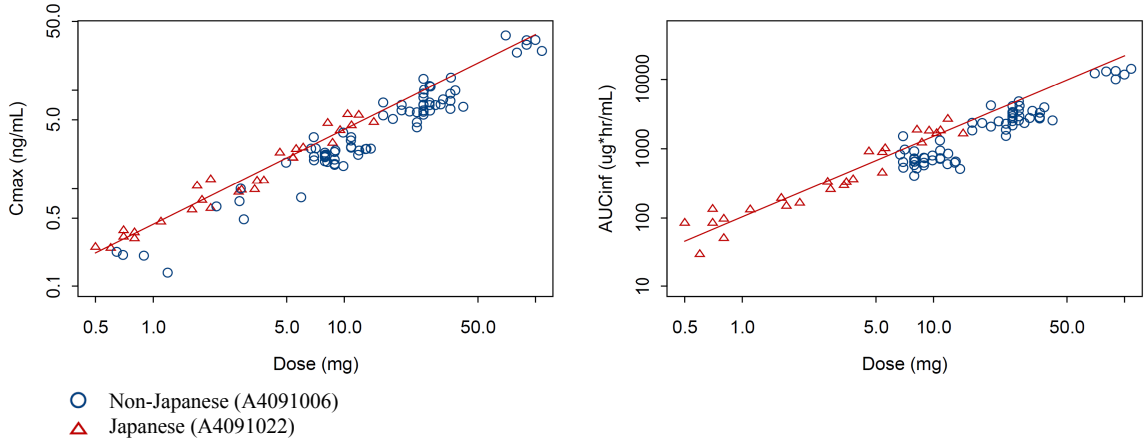
Tanezumab (25, 100, and 200 µg/kg) showed preliminary efficacy against placebo in all the WOMAC subscales (pain, stiffness, and physical function). Of all the tanezumab treatment groups, the percentage of subjects experiencing at least one all-causality adverse event was lowest in the 25 µg/kg treatment group (26.7%) and highest in the 200 µg/kg treatment group (100%). In the placebo treatment group, 13 out of 16 subjects (81.3%) had at least one adverse event. The frequency of overall adverse events was smaller in the combined tanezumab treatment groups (36 out of 67 subjects, 53.7%) than in the placebo treatment group (13 out of 16 subjects, 81.3%). The most frequently reported all-causality adverse event was nasopharyngitis in 9.0% and 31.3% of subjects who received tanezumab or placebo, respectively. Most of the adverse events were mild or moderate in severity. There were no subjects who permanently discontinued the study due to adverse events. Three serious adverse events were reported, and none of these events were considered to be related to the investigational product.

1.2.5. Dose Selection Rationale

Based on the similarity of PK and PK-PD between Japanese and non-Japanese, the same dose selection rationale as study A4091059 was applied for the study.

Individual C_{max} and AUC_{inf} were compared between Japanese (study A4091022, OA subjects) and non-Japanese (study A4091006, OA subjects) populations using non-compartmental analysis data from phase 1/2a studies. PK parameters plotted by the actual total dose for each individual are shown in Figure 1. In Figure 1, linear regression curves were drawn based on parameters from Japanese subjects. The relationship between dose and plasma tanezumab exposure parameters (C_{max} and AUC_{inf}) was almost linear. In addition, individual parameters from Japanese OA subjects were generally within the range of non-Japanese data.

Figure 1. Comparison of individual C_{max} and AUC_{inf} from Studies A4091006 (non-Japanese OA subjects) and A4091022 (Japanese OA subjects) - C_{max} or AUC_{inf} vs. fixed dose (mg)

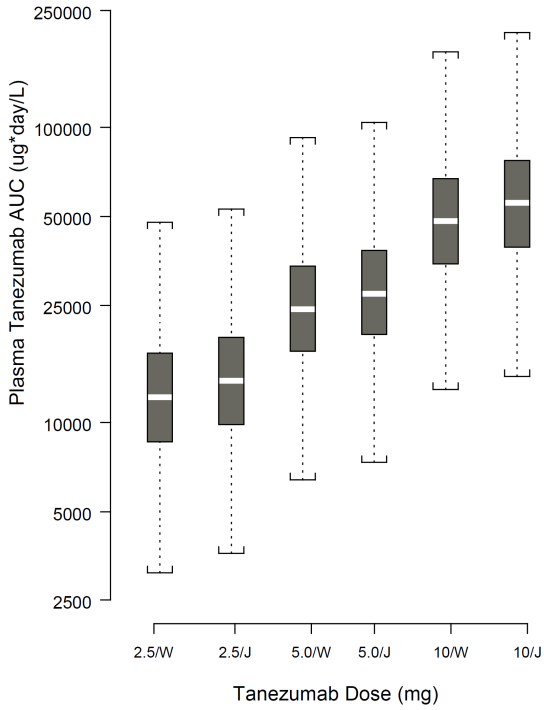


Source:Briefing document for Tanezumab PMDA consultation (8Apr 2010) Appendix 5: Summary of Clinical Pharmacology

Simulations were performed to compare the AUC distribution between Japanese and non-Japanese based on a Japanese/non-Japanese population PK (PopPK) model using data from Japanese (study A4091022) and non-Japanese subjects (A4091006 and A4091008 studies). In the PopPK model, race on PK parameters did not remain as a significant covariate effect.

Figure 2 displays the range of predicted AUCs for the tanezumab doses of 2.5, 5 and 10 mg in both the Japanese and non-Japanese OA populations using the PopPK model. The range of predicted tanezumab AUCs largely overlapped between Japanese and non-Japanese. These simulations based on the PopPK model show that the exposure following an intravenous administration of a fixed dose is comparable between the Japanese and non-Japanese OA subjects.

Figure 2. Simulated AUCs across the doses (fixed dose) for Japanese and non-Japanese OA subjects

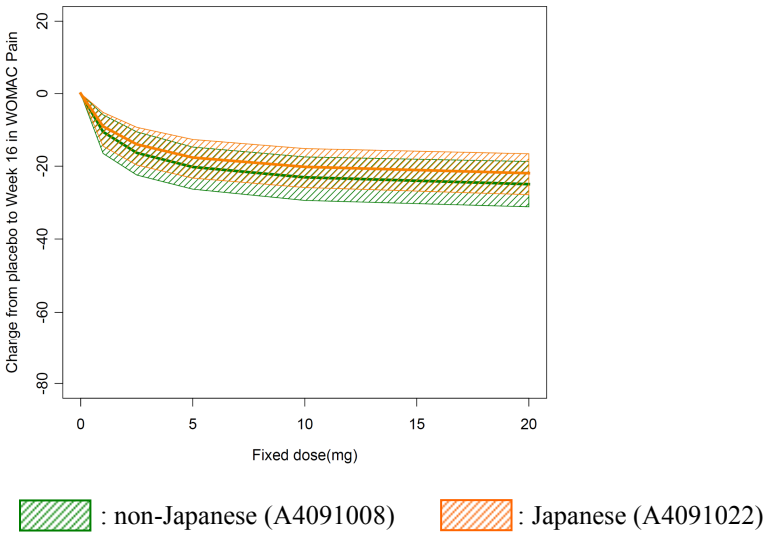


Each box plot indicated the 25% tile (upper quartile, median, lower quartile). W=non-Japanese, J=Japanese
Source: Population modeling analysis report PMAR-00156, Figure 16

The mean dose-response for WOMAC pain change from placebo for Japanese and non-Japanese populations for fixed dose at Week 16 was simulatied based on PK-PD model using WOMAC pain subscale in Japanese (from Study A4091022) and non-Japanese OA (from Study A4091008) subjects. When the dose response was plotted as the change form placebo, the curves overlap further between the populations (Figure 3). As the results of PK-PD

model building, no race effect (Japanese vs. non-Japanese) on each PD parameter was included to the model.

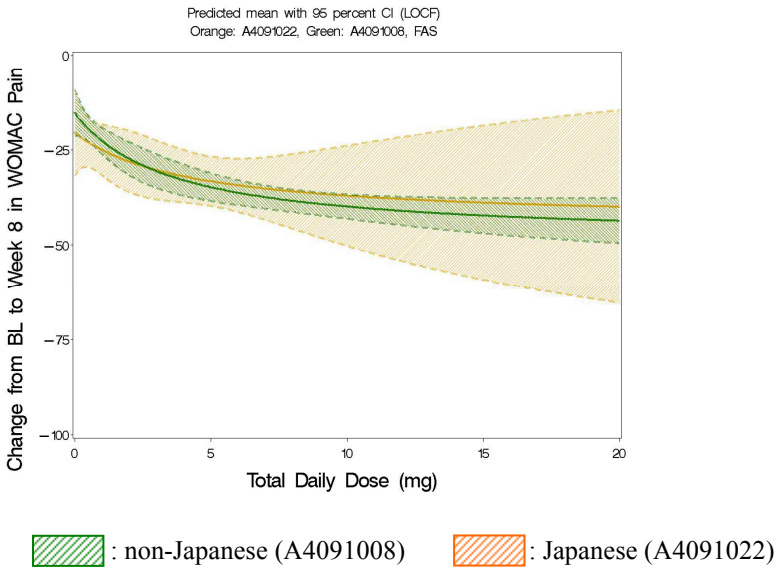
Figure 3. Simulated dose response for WOMAC pain (change from placebo) in typical Japanese and non-Japanese OA patients* at Week 16



95% PI with consideration of RSE for the parameter estimation
*Used typical body weight of 66 kg and 89 kg for Japanese and non-Japanese OA patients, respectively, and mean WOMAC baseline of 60 and 67 for Japanese and non-Japanese OA patients, respectively.
Source: /A409 RN624 tanezumab/A4091022/PKPD Analysis/PMDA BD&TLR/PKPD/dose response/Run18

The relationship between total daily dose and change of WOMAC pain (LOCF) at Week 8 were estimated using E_{max} model besed on results of Study A4091022 and Study A4091008 (Figure 4). This results show a similar trend between Japanese and non-Japanese although limited sample size made large range of 95% CI.

Figure 4. Dose-response relationship based on E_{max} model [relationship between total daily dose and change of WOMAC pain (LOCF) at Week 8]



Source:Briefing document for Tanezumab PMDA consultation (8Apr 2010) Appendix 5: Summary of Clinical Pharmacology

Previous PopPK analyses were conducted to show the similarity in the PK of tanezumab between OA and CLBP subjects and ultimately support the dose regiments for CLBP studies in the non-Japanese. Given the similarity of the PK-PD in Japanese OA subjects to non-Japaese OA subjects, these simulations are also relevant to dose regimen selection for Japanese CLBP subjects.

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. 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 safety and efficacy of a fixed dose of tanezumab 5 mg and 10 mg administered up to 7 times at 8-week intervals relative to an active comparator

treatment group (celecoxib). Patients randomized to the active comparator treatment group will receive celecoxib they were receiving prior to study entry. Patients randomized to receive celecoxib in the current study will receive it at the protocol specified dose (100 mg BID). This dose represents the labeled dose used for the treatment of low back pain in Japan.

1.2.6. Rationale for Celecoxib as an Active Comparator

The primary objective of this study is to evaluate the long-term safety of tanezumab in chronic low back pain patients. The secondary objective is to demonstrate the long-term analgesic efficacy. The long duration of the current study precludes the use of a placebo control group and necessitates the use of an active control group that provides subjects with some degree of efficacy. For most subjects, first line medication options for chronic low back pain are NSAIDs/coxibs and acetaminophen. Celecoxib is selected as an active comparator because celecoxib is commonly used in Japan.

1.2.7. Subject Population Selection Rationale

To facilitate inclusion of an active control treatment group that will serve as a benchmark for evaluation of the long-term safety and efficacy of tanezumab, subjects entering the current study must have moderate to severe chronic low back pain and be experiencing at least some benefit from their current stable dosing regimen of oral NSAID (celecoxib, loxoprofen or meloxicam), be tolerating their NSAID regimen and be taking this medication regularly during the 30-day period prior to the Screening Visit.

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.

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 celecoxib is the Company Core Data sheet.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Objective

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

Secondary Objective

- Demonstrate the long-term analgesic efficacy of tanezumab 10 mg and 5 mg SC administered every 8 weeks (7 administrations).

2.2. Endpoints

2.2.1. Primary Endpoints

Safety Measures

- Adverse events.
- Standard safety assessments (safety laboratory testing [chemistry, and hematology], vital signs).
- Orthostatic (supine/standing) blood pressure assessments.
- Survey of Autonomic Symptoms (SAS) 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.

2.2.2. Secondary Endpoints

Efficacy-Related Endpoints

- Change from Baseline to Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, 56 and 64 in average Low Back Pain Intensity (LBPI) score as measured by an 11-point Numeric Rating Scale (NRS).
- Change from Baseline to Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56 and 64 in the Roland-Morris Disability Questionnaire (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.
- Response as defined by a ≥30%, ≥50%, ≥70% and a ≥90% reduction from Baseline in weekly average LBPI score derived from the subject diary at Weeks 16, 24, 40 and 56.

- Change from Baseline to Weeks 2, 4, 8, 16, 24, 40, 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 16, 24, 40 and 56.

- Treatment Response: Improvement of ≥2 points in Patient's Global Assessment of Low Back Pain at Weeks 16, 24, 40 and 56.

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

- Work Productivity and Activity Impairment Questionnaire: Low Back Pain (WPAI:LBP) change from Baseline to Week 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 64.

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

- Health Care Resource Utilization (HCRU) 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.

2.2.3. Tertiary Endpoints

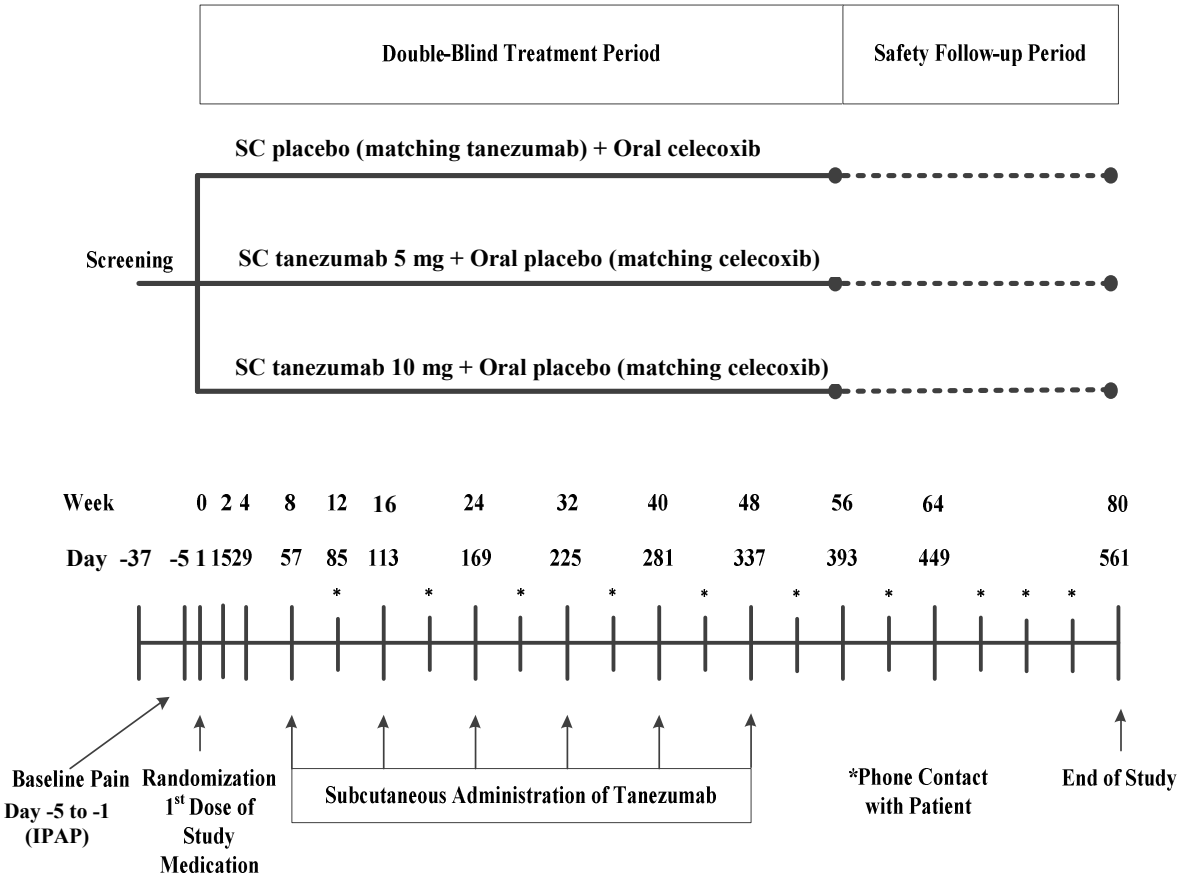
- Plasma tanezumab concentrations.

- Serum NGF assessments.

- Serum and urine osteoarthritis biomarker concentrations.

3. STUDY DESIGN

Figure 5. Study Schematic



This is a randomized, double-blind, active-controlled, multicenter, parallel-group Phase 3 study of the safety and efficacy of tanezumab when administered by SC injection for up to 56 weeks in subjects with chronic low back pain. Subjects will be randomized to 1 of 3 treatment groups in a 1:1:1 ratio. Treatment groups will include:

1. Placebo SC matching tanezumab administered at an 8-week interval (total of 7 times) plus celecoxib 100 mg BID to be administered orally for 56 weeks.

2. Tanezumab 5 mg SC administered at an 8-week interval (total of 7 times) plus placebo matching celecoxib to be administered orally BID for 56 weeks.

3. Tanezumab 10 mg SC administered at an 8-week interval (total of 7 times) plus placebo matching celecoxib to be administered orally BID for 56 weeks.

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 [IPAP]), Double-blind Treatment (56 weeks) and Follow-up (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 IPAP (the 5 days prior to Randomization/Baseline).

Prior to entering the study, subjects must be experiencing some benefit (eg, analgesic effect) from their current stable dose regimen of oral therapy of NSAID (celecoxib 200 mg/day [100 mg BID], loxoprofen 120 to 180 mg/day or meloxicam 5 to 15 mg/day) treatment, be tolerating their NSAID regimen, be taking this medication regularly (defined as an average of at least 5 days per week) during the 30 day period prior to the Screening Visit.

At the Week 16 visit, subjects must have at least a 30% reduction in weekly average LBPI score relative to Baseline and at least a 15% reduction in weekly average LBPI score relative to Baseline at any week from Week 1 to Week 15 in order to continue investigational product. Subjects who do not meet these response criteria will be discontinued from the Treatment Period and enter the 24-week Early Termination Follow-up Period (See Section 6.9.1).

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.

For subjects who withdraw from the study, see Section 6.9.1. Every effort should be made to have the subject agree to complete the entire 24-week Early Termination Safety Follow-up.

Details relevant to the study design can be found in Sections 6 and 7 and the SUBSTUDY SCHEDULE OF ACTIVITIES (Appendix 18, Table 7)

4. SUBJECT SELECTION

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

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. Japanese males or females, ≥18 years of age.

3. Duration of chronic low back pain for ≥3 months.

4. Treatment with agents for low back pain for ≥3 months.

5. 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).

6. Be experiencing some benefit from their current stable dose regimen of oral therapy of NSAID (celecoxib 200 mg/day [100 mg BID], loxoprofen 120 to 180 mg/day or meloxicam 5 to 15 mg/day) treatment, be tolerating their NSAID regimen, be taking this medication regularly (defined as an average of at least 5 days per week) during the 30 day period prior to the Screening visit and must have had some improvement in low back pain, but still require additional pain relief at Screening.

7. Maintain a stabilized dose regimen of celecoxib 100 mg BID with a minimum compliance of 70% (ie, 5 of 7 days per week) for at least the final 2 weeks (subjects who were receiving celecoxib as pre-study treatment) or 3 weeks (subjects who were receiving loxoprofen or meloxicam as pre-study treatment) of the Screening period directly prior to the Baseline (Day 1) visit.

8. LBPI score of ≥5 at Screening (See Section 7.1.1).

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

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

11. Subjects must be willing to discontinue all pain medications for chronic low back pain except rescue medication and investigational product and not use prohibited pain medications throughout the duration of the study except as permitted per Protocol (refer to Section 5.8.1 for details regarding prohibited medications).

12. 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).

13. 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.

14. 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 with any of the following characteristics/conditions 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 >39 kg/m^2.

3. Diagnosis of osteoarthritis of the knee or hip as defined by the 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, or any closed claim within the past 5 years.

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, or 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 the relevant oral celecoxib the subject could be randomized to receive or any of its excipients or existence of a medical condition or use of concomitant medication for which the use of celecoxib is contraindicated (refer to product labeling).

19. 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).

20. Use of prohibited medications or prohibited non-pharmacological treatments without the appropriate washout period (if applicable) prior to Screening or IPAP. 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 ≥160 mmHg in systolic pressure or ≥100 mmHg 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 blood pressure 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 (SAS) (See Appendix 15).

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]).[20] 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 called into the Interactive Response Technology (IRT) system at the Baseline visit:

1. Subject must have completed appropriate washout of analgesics;

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

3. Subjects must have maintained a stabilized dose regimen of celecoxib 100 mg BID with a minimum compliance of 70% (ie, 5 of 7 days per week) for at least the final 2 weeks (subjects who were receiving celecoxib as pre-study treatment) or 3 weeks (subjects who were receiving loxoprofen or meloxicam as pre-study treatment) of the Screening period directly prior to the Baseline (Day 1) visit.

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

5. Subjects must meet the Baseline LBPI score and Patient's Global Assessment of Chronic Low Back Pain Baseline requirements (Inclusion Criteria 9 and 10).

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

7. 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 prohibited and permitted medications.

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 investigational product and followed as described in Section 6.9.2.

All female subjects who are of child-bearing potential and are sexually active and at risk for pregnancy, must agree to use two (2) methods of highly effective contraception consistently and correctly for the duration of the active treatment period and for 112 days (16 weeks) after the last dose of SC investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that 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 or her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the schedule of activities and document such conversation in the subject's chart. In addition, the investigator or his or her designee will instruct the subject to call immediately if the selected contraception methods are discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

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

1. Established use of oral, inserted, injected, implanted, or transdermal hormonal methods of contraception is allowed provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper containing intrauterine device (IUD).

3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, 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 postvasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

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

4.5. Sponsor 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 numbers, contact information for the investigational site, and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational

site and the study team are not available. It is therefore intended to augment, but not replace the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

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

5.1. Allocation to Treatment

Subjects will be randomized at Baseline to one of the following treatment groups, all subjects will receive SC and PO treatment during the Double-blind Treatment period of the study:

Table 4. Study Treatments

Treatment Group	Subcutaneous Investigational Product (SC)	Oral Investigational Product (PO)
1	Placebo for tanezumab once every 8 weeks x 7 doses	Celecoxib 100 mg BID through Week 56
2	Tanezumab 5 mg once every 8 weeks x 7 doses	Placebo for celecoxib through Week 56
3	Tanezumab 10 mg once every 8 weeks x 7 doses	Placebo for celecoxib through Week 56

Subjects will be randomly assigned in a 1:1:1 ratio to the above treatment regimens according to a computer generated randomization code. The randomization will not be stratified. Randomization will be coordinated centrally through IRT. The system will provide subject identification numbers at Screening, which will subsequently be 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 will be provided in the Pharmacy Manual.

5.2. Breaking the Blind

This is a randomized, double-blind, 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 celecoxib 100 mg or corresponding placebo (SC or PO) 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.

For oral celecoxib treatments (celecoxib or corresponding placebo) and rescue medication (acetaminophen/paracetamol), compliance will be reviewed and reconciled at each study visit. For oral investigational product (celecoxib or matching placebo), investigators should encourage subjects to maintain 100% compliance. If a subject's overall compliance with oral investigational product 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. The use of non-study NSAIDs is prohibited during the study except as described in Section 5.8.1.2.

Protocol rules governing the use of rescue medication are described in Section 5.9.

5.4. Drug Supplies

5.4.1. Dosage Form(s) and Packaging

Tanezumab, placebo for tanezumab, celecoxib and placebo for celecoxib 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 PFS. Each PFS contains a sufficient amount of tanezumab to provide the intended dose of drug at a concentration of 10 mg/mL.

Each PFS is packed in an individual carton. Each PFS has a unique container number.

5.4.1.2. Placebo for Tanezumab

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

5.4.1.3. Non-steroidal Anti-inflammatory Drugs (NSAID)

5.4.1.3.1. Celecoxib 100 mg

Celecoxib will be provided as oral capsules containing 100 mg of active celecoxib. Celecoxib 100 mg will be packaged in high-density polyethylene (HDPE) bottles with child resistant closures. The bottles used for the screening period contain 80 capsules (open-label supply) and the bottles used for the treatment period contain 70 capsules (double-blind supply).

5.4.1.3.2. Placebo to match celecoxib 100 mg

Placebo for celecoxib will be provided as oral capsules matching those used for celecoxib 100 mg capsules. Placebo to match celecoxib 100 mg will be packaged in HDPE bottles with child resistant closures containing 70 capsules (double blind supply).

5.4.1.4. Acetaminophen/paracetamol (Rescue Therapy)

Acetaminophen/paracetamol tablets will be issued by the study sites in its approved marketed product dress. Any approved commercial product of acetaminophen/paracetamol tablet is permitted.

5.4.2. Preparation and Dispensing

See the Dosage and 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 per Japan regulations.

5.5. Administration

5.5.1. SC Investigational Product Administration

Tanezumab or matching placebo for tanezumab will be administered via SC injection by a medical staff (as per Japan regulations) and where facilities to handle allergic reactions are available. All subjects will receive 1 mL of investigational product administered as a SC injection. Subcutaneous injections are to be administered in the abdomen or anterior aspect of the thigh. Selection of the SC injection site for each injection will be at the discretion of the investigator taking into account subject preferences when possible. The SC injection should not be administered in areas where the skin is burned, reddened, inflamed, swollen, or scarred. All Japan regulations must be complied with in assigning administration duties.

5.5.2. Oral Investigational Product Administration

During the Screening period of the study, subjects will be provided with celecoxib and will maintain a stabilized dose regimen of celecoxib 100 mg BID for at least the final 2 weeks (subjects who were receiving celecoxib as pre-study treatment) or 3 weeks (subjects who were receiving loxoprofen or meloxicam as pre-study treatment) of the Screening period

directly prior to the Baseline (Randomization/Day 1) visit. Subjects should be advised to take their morning dose of this celecoxib before arriving for the Randomization/Day 1 clinic visit.

Celecoxib 100 mg or corresponding placebo will be self-administered by subjects orally twice a day (morning and evening) during the double-blind treatment period of the study. On Study Day 1, a morning dose of oral investigational product (celecoxib or corresponding placebo) will not be administered to or taken by subjects. The first dose of oral investigational product will be self administered by subjects on the evening of Day 1. On the days of all other clinic visits (Weeks 2, 4, 8, 16, 24, 32, 40, 48 and 56), subjects should be advised to take their morning dose of celecoxib or corresponding placebo at home prior to the clinic visit.

5.6. Investigational Product Storage

The investigator or an approved representative (eg, Pharmacist) will ensure that all investigational products, including any comparative agents and/or marketed products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the label. See the Pharmacy Manual for storage conditions of the product.

Storage conditions stated in the single reference safety document (SRSD) (ie, investigator's brochure [IB]; core data sheets [CDS]), will be superseded by the storage conditions stated in the labeling.

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

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

product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation.

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

Site staff will instruct subjects on the proper storage requirements for take home investigational products.

5.7. Investigational Product 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.

5.7.1. Destruction of Investigational Product Supplies

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

5.8. Concomitant Treatment(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 (Refer to Appendix 4) other than investigational product (eg, TNF-α inhibitors such as adalimumab, etanercept, infliximab), including any live vaccines, within 3 months of the IPAP or 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 Period 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:

- Aspirin at doses >324 mg/day or salicylate containing medications.

- Opioid analgesics are prohibited beginning 48 hours prior to the start of the IPAP through Week 64.

As specified in Section 5.8.2, occasional use of medication to relieve pain is permitted in certain situations. Use of NSAIDs and COX-2 selective inhibitors (outside of oral investigational product), both prescription or over-the-counter (OTC) is prohibited through the Week 64 visit.

Using IRT, subjects will record the number of days of concomitant NSAID use weekly 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 on a CRF. Subjects who report concomitant use of prescription or OTC NSAIDs during the study will be managed as per the following guidelines:

- Subjects who report concomitant use of NSAID should be interviewed by study site personnel to determine reason for use and if the subject anticipates being able to comply with concomitant medication restrictions in the future. Subjects who indicate they are taking NSAIDs because of insufficient chronic low back pain relief or who indicate that they cannot or will not be able to comply with concomitant medication restrictions will be withdrawn from investigational product and entered in the Early Termination Follow-up period (Refer to Section 6.9).

- Subjects who reported greater than 10 days (aggregate total) of concomitant NSAID use (any dosage of NSAIDs, for conditions other than chronic low back pain) in a SC dosing interval (defined as the period of 8 weeks between 2 SC doses) and who after counseling report further concomitant NSAID use should be withdrawn from investigational product and entered in the Early Termination Follow-up period (Refer to Section 6.9).

Subjects will be instructed that many OTC medications contain NSAIDs and to be aware of this during their selection of OTC medications.

5.8.1.3. Prohibited Medications from Washout until Week 16

In addition to the prohibited medications listed in Sections 5.8.1.1 and 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 investigational product (tanezumab and celecoxib) and provided rescue medication (acetaminophen/paracetamol). Use of analgesics except celecoxib as investigational product and acetaminophen/paracetamol are prohibited beginning 48 hours prior to the start of the IPAP (the 5 days prior to Randomization/Baseline) or at the period of time prior to the start of the IPAP 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 OTC products and to report their use as concomitant medications.

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

To investigate the response criteria (see Sections 3 and 6.4.5), initiation of the following medicines is prohibited through Week 16. However, subjects who have taken a stable dose of these medications for at least 30 days prior to Screening will be allowed to continue their regimen.

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

- Pregabalin and gabapentin are prohibited beginning within 48 hours prior to the start of the IPAP (the 5 days prior to Randomization/Baseline) .

- All anti-depressants for the treatment of depression are prohibited beginning within 30 days prior to Screening (Refer to Appendix 4).

- Anti-depressants prescribed for the treatment of chronic low back pain are prohibited beginning 48 hours to start of the IPAP or at the period of time prior to the start of the IPAP that is 5 times the half-life of the particular anti-depressant, whichever is greater.

- Centrally acting agents such as sedatives/hypnotics, anxiolytics, tranquilizers, or benzodiazepines are prohibited beginning within 30 days prior to the Screening (Refer to 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 IPAP until Week 16. Subjects should be advised that St. John's wort may interfere with the efficacy of hormonal contraceptive products.

5.8.1.4. Prohibited Non-pharmacological Therapies

To investigate the response criteria (see Sections 3 and 6.4.5), initiation of non-pharmacological therapies is prohibited through Week 16.

- Commencing of physiotherapy is not allowed from the beginning of the IPAP 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 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 IPAP (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.

- Low-dose aspirin therapy for cardiac prophylaxis (≤324 mg per day).

- After the Week 16 visit, subjects may initiate skeletal muscle relaxants, pregabalin, gabapentin, benzodiazepines, sedative/hypnotics, anxiolytics and anti-depressants, herbal, homeopathic, and naturopathic remedies and topical analgesics (except for NSAIDs and Opioids [eg, Fentanyl and Buprenorphine]). However, the analgesics for chronic low back pain (NSAIDs and opioids, Refer to Appendix 4) except investigational product (tanezumab and celecoxib) are prohibited through Week 64. Subjects should be counseled to consult with the study site before initiating any new therapy and investigators should evaluate any new therapy for potential adverse interactions with celecoxib or rescue therapy by consulting the product labeling. Furthemore, subjects who have taken a stable dose of these products for at least 30 days prior to Screening will be allowed to continue their regimen.

- 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 investigational product provided 16 weeks have elapsed since the last dose of SC investigational product. In this study, standard of care treatment refers to analgesics or other treatments approved by MHLW 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 investigational product but the cost of pre-specified analgesics will be paid for by Pfizer 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 tablets).

During the Washout Period and the IPAP (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 investigational product and entered in the Early Termination Follow-up Period (See Section 6.9.1). 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 investigational product.

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 national labeling.

Up to 16 weeks after the last dose of SC investigational product, 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 approximately 16 weeks after the last SC dose of investigational product, 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 national labeling.

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

Subjects will be instructed that many OTC 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

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

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

The study visit windows are ±2 days for the 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 ±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. 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 investigational product 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 to any study visit at which efficacy data is collected.

6.1. Screening Period

The Screening period will consist of a maximum of 37 days prior to Randomization and will last a minimum of 2 or 3 weeks (14 or 21 days). The 2 or 3-week minimum Screening period is needed to complete the 2-week period of pre-randomization, celecoxib regimen stabilization. The length of the celecoxib regimen stabilization period will depend on the NSAID subjects are receiving in the 30 days prior to screening. The celecoxib regimen stabilization period will be a minimum of 2 weeks if the pre-study NSAID is celecoxib or a minimum of 3 weeks if the pre-study NSAID is loxoprofen or meloxicam. Prior to entering the IPAP, subjects taking prohibited medications must complete the required washout from these medications for at least 5 half-lives or 48 hours (whichever is greater). Screening procedures should be staged to minimize burden to the subject and minimize conduct of procedures that may not be required if a subject is found to be ineligible. To assist in this staging, screening procedures have been sorted into Screening Stage 1 and Screening Stage 2.

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

Subject demographics and the date of onset and primary etiology of primary diagnosis (chronic low back pain) will be obtained. A comprehensive medical history and concomitant medication review will be performed for each subject; in addition, a comprehensive evaluation of musculoskeletal history and musculoskeletal physical exam will be performed (refer to Section 7.3.1.2). 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 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. Screening Period Stage 1 (Initial Screening Visit):

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

6.1.2. Screening Period Stage 2

Subjects who satisfy inclusion/exclusion criteria (to this point) and for whom radiographic eligibility has been confirmed will undergo the following screening procedures:

- Subjects will be instructed in the use of the IRT system to record daily (during IPAP) /weekly LBPI scores, daily/weekly rescue medication use, weekly joint pain entries,

weekly concomitant NSAID (outside of oral investigational product) use entries with specific instructions as when to test the system and when to begin entering data.

- Subjects will maintain the BID dosing regimen of celecoxib 100 mg for at least the final 2 or 3-weeks (average of 5 of 7 days per week at minimum; ie, minimum 70% compliance) of the Screening period directly prior to the Baseline (Day 1) visit.

NOTE: Beginning at Screening, subjects should use study-supplied oral investigational product (celecoxib during Screening and celecoxib or matching placebo post-randomization) through Week 56.

Subjects who were receiving celecoxib will receive the same oral celecoxib but may need to change dosing regimen to a BID dosing regimen for the duration of the study. Subjects must maintain the BID dosing regimen of celecoxib 100 mg for at least the final 2 weeks of the Screening period directly prior to the Baseline (Randomization/Day 1) Visit.

Subjects who were receiving loxoprofen or meloxicam prior to Screening will discontinue their prior NSAID and begin celecoxib dosing during the Screening period. Subjects will use celecoxib for the remainder of the Screening period and will be stabilized on a dosing regimen of celecoxib 100 mg BID for at least the final 3 weeks of the Screening period directly prior to the Baseline (Randomization/Day 1) visit.

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 IPAP 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 the study monitor for guidance.

6.3. Initial Pain Assessment Period

The IPAP 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 IPAP 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. Double-Blind Treatment Period

The Double-blind Treatment period begins with the Baseline (Day 1) visit and concludes with completion of the Week 56 visit procedures. The Double-blind Treatment period is 56 weeks in duration and consists of 10 clinic visits (Day 1 and Weeks 2, 4, 8, 16, 24, 32, 40, 48 and 56) and 6 telephone contacts (Weeks 12, 20, 28, 36, 44 and 52) between site staff and study subjects.

6.4.1. Baseline Visit (Day 1)

6.4.1.1. 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. Full eligibility, including (but not limited to) confirmation of appropriate washout of concomitant medication, compliance with celecoxib treatment regimen stabilization, abstinence from acetaminophen/paracetamol in the previous 24 hours, completion of at least 4 LBPI scores on the daily pain diary in the 5 days prior to the Baseline visit, required LBPI and PGA of LBP scores and that no adverse events occurred since signing informed consent that would render the subject ineligible for randomization, should be assessed before carrying out randomization in the IRT system.

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

6.4.1.2. Dosing (Day 1)

Subjects will receive a single SC injection of blinded investigational product 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 Japanese 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.

6.4.1.3. Post Dosing (Day 1)

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

- Review and record Adverse Events.

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

6.4.2. Week 2 and 4 Visits

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

6.4.3. Week 8 Dosing Visit

The subject will return for clinic visits at Week 8 to be assessed for efficacy and safety. Refer to Schedule of Activities Table 1 for the procedures to be performed at the Week 8 Visit.

The dosing and post-dosing procedures are the same as those as described in Section 6.4.1.2 and 6.4.1.3.

6.4.4. Week 12 Telephone Visit

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

Refer to Schedule of Activities Table 1 for the procedures to be performed at the Week 12 Telephone Contact.

6.4.5. Week 16 Dosing Visit

The subject will return for clinic visits at Week 16 to be assessed for efficacy and safety.

Treatment response will be calculated by the IRT. Subjects must have ≥30% reduction in weekly average LBPI score relative to Baseline and ≥15% reduction in weekly average LBPI score relative to Baseline at any week from Week 1 to Week 15, in order to continue investigational product. Subjects who do not meet this response criterion will be discontinued from the Treatment Period and will enter the 24 week Early Termination Follow-up (See Section 6.9).

Refer to Schedule of Activities Table 1 for the procedures to be performed at the Week 16 Visit.

The dosing and post-dosing procedures are the same as those as described in Section 6.4.1.2 and 6.4.1.3.

6.4.6. Weeks 20 Telephone Visit

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

Refer to Schedule of Activities Table 1 for the procedures to be performed at the Week 20 Telephone Contact.

6.4.7. Week 24 Dosing Visit

The subject will return for clinic visits at Week 24 to be assessed for efficacy and safety. Refer to Schedule of Activities Table 1 for the procedures to be performed at the Week 24 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. 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 confirmation of continued radiographic eligibility from the Central Reader.

The dosing and post-dosing procedures are the same as those as described in Sections 6.4.1.2 and 6.4.1.3.

6.4.8. Weeks 28, 36, 44 and 52 Telephone Visits

The subject will be contacted by telephone at Week 28, 36, 44 and 52 to review adverse events, concomitant medications, compliance with weekly IRT entries and to remind female subjects of contraceptive requirements.

Refer to Schedule of Activities Table 1 for the procedures to be performed at the Week 28, 36, 44 and 52 Telephone Contacts.

6.4.9. Weeks 32, 40 and 48 Dosing Visits

The subject will return for clinic visits at Week 32, 40 and 48 to be assessed for efficacy and safety. Refer to Schedule of Activities Table 1 for the procedures to be performed at the Week 32, 40 and 48 Visits.

The dosing and post-dosing procedures are the same as those as described in Section 6.4.1.2 and 6.4.1.3.

6.4.10. Week 56 Visit-End of Treatment Visit

The subject will return for clinic visits at Week 56 to be assessed for efficacy and safety. Refer to Schedule of Activities Table 1 for the procedures to be performed at the Week 56 Visit.

Radiographic assessment (X-rays) of hips, knees, and shoulders, and any major other 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.

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

6.5. Week 60 Telephone Visit

The subject will be contacted by telephone at Week 60 to review adverse events, concomitant medications, compliance with weekly IRT entries and to remind female subjects of contraceptive requirements.

Refer to Schedule of Activities Table 2 for the procedures to be performed at the Week 60 Telephone Contact.

6.6. Week 64 Visit-Safety Follow-up Period

The subject will return for clinic visits at Week 64 to be assessed for efficacy and safety. Refer to Schedule of Activities Table 2 for the procedures to be performed at the Week 64 Visit.

6.7. Weeks 68, 72, and 76 Telephone Visits

The subject will be contacted by telephone at Week 68, 72 and 76 to review adverse events, concomitant medications and compliance with weekly IRT entries.

Refer to Schedule of Activities Table 2 for the procedures to be performed at the Week 68, 72 and 76 Telephone Contacts.

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).

6.8. Week 80 Visit-End of Study Visit

The subject will return for clinic visits at Week 80 to be assessed for safety. Refer to Schedule of Activities Table 2 for the procedures to be performed at the Week 80 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.

6.9. 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 subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return 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 investigational product.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponser 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 6.9.1. In addition, subjects will be asked about the presence and severity of joint pain (hips, knees and shoulders), rescue medication use, and NSAID (outside of oral investigational product) 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 scheduled first visit, which is to occur 8 weeks after the last dose of investigational product (as described in 6.9.1.1).

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 investigational product to collect safety and efficacy data. Once the clinic visit 16-weeks after the last administration of SC investigational product 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 investigational product. That visit, (described in 6.9.1.5), 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 .investigational product. 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, a general physical examination, TSQM, mPRTI 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 investigational product.

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 investigational product, 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 investigational product, respectively). After the second Early Termination Follow-up visit occurring approximately16 weeks after the last SC dose of investigational product, subjects may be started on standard of care treatments for low back pain. Subjects may continue to use acetaminophen/paracetamol as needed up to 3000 mg per day.

6.9.1. Early Termination Follow-up Procedures

6.9.1.1. Early Termination Follow-up Period Visit 1 (8 weeks after the last dose of SC Investigational Product)

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

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.

6.9.1.2. Early Termination Follow-up Period Telephone Visit 1 (12 weeks after last dose of SC investigational product)

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

Refer to the Early Termination Schedule of Activities Table 2 for the procedures to be performed at the Early Termination Follow-up Period Telephone Contact 1, to remind female subjects of contraceptive requirements.

6.9.1.3. Early Termination Follow-up Period Visit 2 (16 weeks after last dose of SC investigational product)

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

6.9.1.4. Early Termination Follow-up Period Telephone Visit 2 (20 weeks after last dose of SC investigational product)

The subject will be contacted by telephone (20 weeks after the last dose of SC investigational product) to review adverse events, concomitant medications, compliance with weekly IRT entries at Telephone contact 2.

Refer to the Early Termination Schedule of Activities Table 2 for the procedures to be performed at the Early Termination Follow-up Period Telephone Contact.

6.9.1.5. Early Termination Follow-up Period Visit 3 (24 Weeks after last dose of SC investigational product)

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

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.

6.9.2. 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 investigational product.

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 A4091063 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 6.4.10 and 6.6); 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 6.8). 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 investigational product.

- 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 6.9) 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 6.9) 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 investigational product 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 investigational product 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 that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Subject Collected Efficacy Assessments

7.1.1. 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 on a daily basis during the IPAP then assessed weekly from Baseline through to Week 64 or Early Termination Visit 2.

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 11).

Example Question:

"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."

7.1.2. Rescue Medication and Amount

Rescue medication use will be collected daily via IRT from the beginning of the IPAP to the Week 16 Visit. The dosage strength of the acetaminophen/paracetamol tablets will be captured. The subject should note the number of tablets 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.[21] The score for the index ranges from 0 to 24 with a lower score indicating better function. All subjects will complete the RMDQ via IRT at the study center at Baseline, and Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56 and 64 (or Early Termination visits 1 and 2) 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 8) 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 visits (or Early Termination visits 1 and 2). 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, 40, 56 and 64 (or Early Termination Visits 1 and 2) visits. Refer to Appendix 9 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 10) prior to SC dosing at Baseline, Week 16 , 56 and 64 (or at Early Termination Visits 1 and 2). 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.[22] 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 12). 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.[23] The 5-item Health State Profile and the VAS will be administered in this study at Baseline, Weeks 16 and 56 (or at Early Termination Visits 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 17) via IRT at Weeks 16 and 56 (or at Early Termination Visit 1).

The TSQM is an 11-item validated scale that quantifies the subject's level of satisfaction with investigational product, 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.[24]

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 investigational product. In this study, three items are being collected: previous treatment, preference and willingness to continue using the investigational product. Higher scores indicate greater satisfaction, preference or willingness to use the investigational product; see Appendix 16. The questionnaire will be self-completed by the subject using IRT at Week 16 and Week 56 or at Early Termination Visit 1.

7.2.8. Health Care Resource Utilization (HCRU)

The HCRU (eg, doctor office visits, hospitalizations, surgeries or procedures) during the 3 month period prior to Baseline will be collected by a questionnaire via IRT. In addition, HCRU will be collected at study visits at baseline, Week 64 and Week 80 (or at Early Termination, Visits 2 and 3).

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), 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, Week 56 or at Early Termination Visit 1.

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 Visits). 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 range of 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, ankles 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 IPAP 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 OTC or prescription NSAID (outside of oral investigational product) use will be collected weekly via IRT from Screening period Stage 2 visit until the Week 80 visit. During the Early Termination Follow-up Period, for subjects who discontinue treatment, the use of

OTC 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, 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	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 (eg, for opiates, barbiturates, amphetamines, cocaine, propoxyphene, methadone, phencyclidine, and methaqualone). Screening, Weeks 56 and 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	Screening only: pH, protein, glucose, ketones, blood, bilirubin, nitrite, specific gravity and leukocytes. Microscopic analysis performed if abnormalities are present on the above components.
Does not include PK, PD (NGF), ADA and biomarkers (refer to sections below for collection details).			

7.3.4.1. 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). 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).

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-tanezumab 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 and 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 Testing

For female subjects of childbearing potential, a serum pregnancy test, with 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[CCI] 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 Week 56 and 64 (to confirm the subject has not become pregnant during the study period) or at Early Termination Visits 1 and 2. Pregnancy tests will also be done whenever 1 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 Japanese regulations. [CCI]

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 post-menopausal 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, 56, 64 and 80 (or at Early Termination). 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 Early Termination). At each of these clinic visits, blood pressure will be assessed in supine and standing positions. Orthostatic blood pressure measurements will be obtained after collection of the sitting vital signs and before any required phlebotomy (and prior to dosing at dosing visits). To minimize chances of orthostatic hypotension related to volume depletion, subjects should be reminded to report for clinic visits well hydrated. In this regard, investigators could consider recommending to subjects that they consume 8‑16 ounces (240‑480 mL) of water prior to reporting to the clinic for study visits. All orthostatic blood pressure measurements will be recorded in the IRT system.

Supine blood pressure measurement will be obtained after subjects have been in the supine position for a minimum of 10 minutes. To ensure that a stable supine blood pressure measurement is obtained, at least two systolic and diastolic measurements will be performed. If the replicate systolic and diastolic measurements differ by no more than 10 mmHg and 5 mmHg, respectively, the supine blood pressure will be considered to be stable. The mean of the two stable replicate measures will be considered to represent the baseline supine blood pressure (mean systolic and mean diastolic blood pressure) for that visit. Once the supine blood pressure is considered to be stable, subjects will be asked to assume the standing position. After subjects have been in the standing position for 1 minute and 3 minutes, systolic and diastolic blood pressure will be measured and recorded for both timepoints. If the measurements do not meet the criteria for orthostatic (postural) hypotension, no further measurements are needed. If either the 1 minute or 3 minute standing blood pressure measurements show decreases meeting the criteria shown in Table 5, the sequence of supine and standing measurements should be repeated up to 2 more times. Refer to Table 5 for the criteria defining orthostatic hypotension and actions that should be taken when orthostatic hypotension criteria are met.

Table 5. 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 minutes standing BP meets the orthostatic (postural) hypotension criteria, then that sequence is considered positive. If 2 of 2 or 2 of 3 sequences are positive, then orthostatic hypotension is considered confirmed and an adverse event of orthostatic hypotension will be reported. - Refer to Section 7.4.3 for subject management and dosing guidance.
OR		
>150 mmHg	≥30 mmHg systolic **or** ≥15 mmHg diastolic	

Refer to Section 7.4.3 for guidance on determining which subjects with confirmed orthostatic hypotension will require consultation with a neurologist or cardiologist.

7.3.6. 12-Lead Electrocardiogram

A 12-lead ECG will be performed at Screening, Weeks 16, 56 and 80 (or Early Termination Visits 1 and 3) 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 investigational product. 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 (SAS)

The Survey of Autonomic Symptoms (SAS) 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 15).

Subjects will complete the SAS at Screening, prior to SC dosing at Weeks 24, 56 and 80 (or at Early Termination Visits 1 and 3). 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 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 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). 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 discontinued 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 6.9.1) 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 6.9.1.5) after the last dose of SC investigational product 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.[25,26] 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) and the Neuropathy Impairment Score (NIS) will be completed at these time points based on this neurological exam (refer to Appendix 7). Neurologic examination will assess strength of groups of muscles of the head and neck, upper limbs and lower limbs, deep tendon reflexes and sensation (tactile, vibration, joint position sense and pin prick) of index fingers and great toes in order to complete the NIS. The NIS is a standardized instrument which has been tested in both healthy subjects and patients with neuropathy and which has been used to evaluate subjects for signs of peripheral neuropathy in clinical trials.[27] 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 participation in the study, or 4) an adverse event of severe intensity.

- A new or worsened clinically significant abnormality on the neurologic exam should be reported as an adverse event and may result in a neurologic evaluation/consult further to the guidance above.

- A neurological adverse event which is non-neuropathic (eg, stroke, seizure) but which the investigator considers medically important should also result in a neurological consultation.

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

7.3.10.1. Serum for Analysis of Anti-Drug Antibodies (ADA) Against Tanezumab

Blood samples for the assessment of ADA against tanezumab (anti-tanezumab antibodies) will be collected at Baseline (Day 1; pre-dose) and Weeks 8 (pre-dose), 16 (pre-dose), 32 (pre-dose), 48 (pre-dose), 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 investigational product was administered (or at 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.

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

7.4. Triggered Requirements and Subject Level Stopping Rules

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

7.4.1. Dysesthesia/Allodynia

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

Unresolved dysesthesia/allodynia: Withhold the SC investigational product for a maximum of 14 days beyond the planned dosing day to allow for resolution of the adverse event. If the dysesthesia/allodynia has not resolved within the 14-day period after the scheduled dosing

date, the subject will not receive any additional doses of investigational product and will enter the Early Termination Follow-up Period (see Section 6.9).

7.4.2. Hypersensitivity or Injection Site Reactions

If a severe hypersensitivity reaction or severe injection reaction occurs following any administration of SC investigational product, the investigational product should be discontinued immediately and no further administrations of SC investigational product will be allowed. Subjects experiencing these types of reactions will enter the Early Termination Follow-up Period (see Section 6.9).

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 investigational product should occur. Figure 6 provides a flow diagram for the processes described below.

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

2. If an apparent medical cause is identified at the time the orthostatic hypotension criterion is met or if 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.

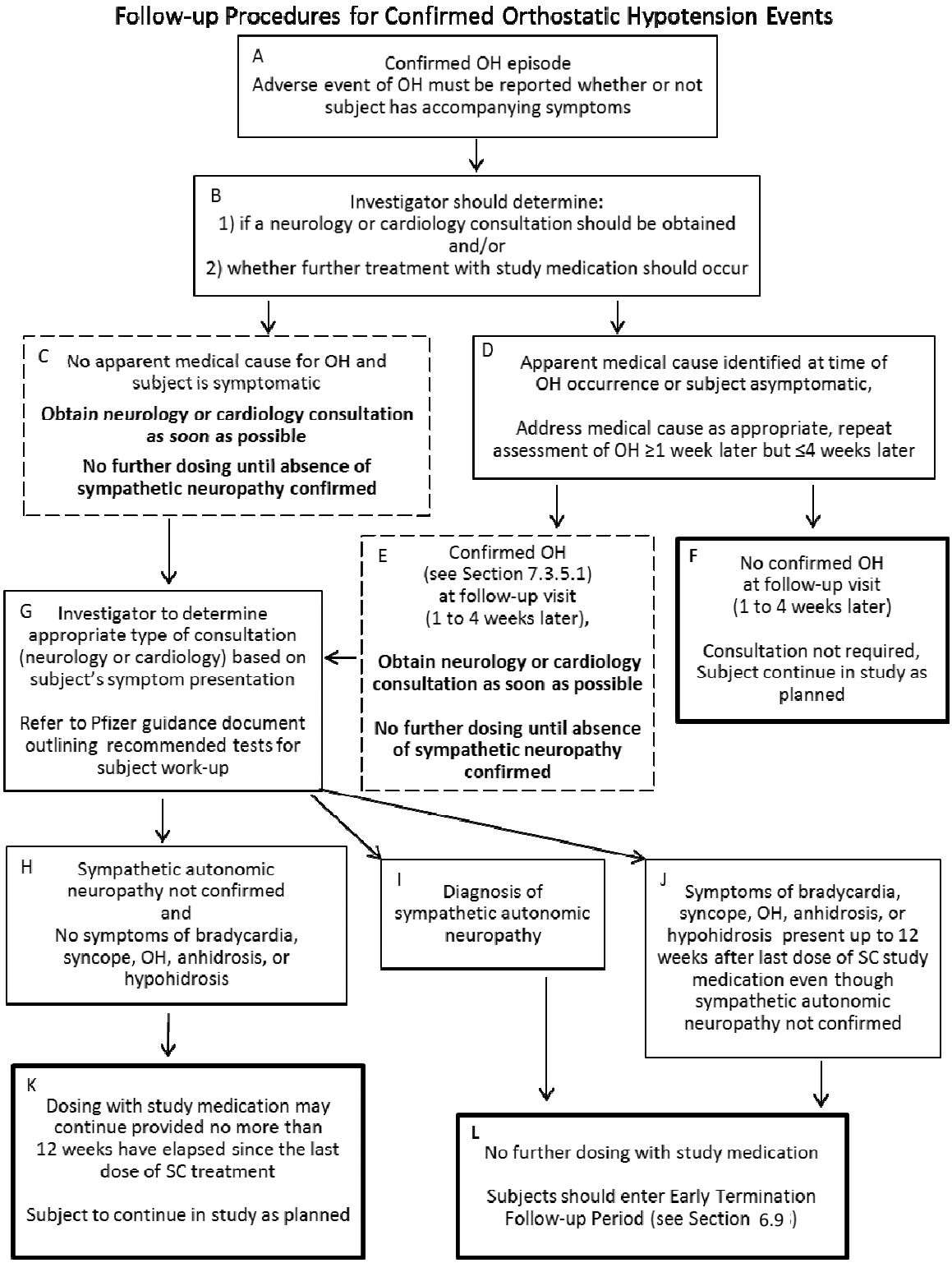
Sympathetic function adverse events: Subjects reporting adverse events (any seriousness or severity) with preferred terms of bradycardia (see Section 7.3.6 for ECG criteria for

bradycardia), syncope, orthostatic hypotension (as described above and in boxes C and E of flow diagram Figure 6), 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 investigational product until the absence of sympathetic autonomic neuropathy has been confirmed. Subjects who are not deemed to have a sympathetic autonomic neuropathy based on this evaluation can continue the study provided no more than 12 weeks have elapsed since the last dose of SC treatment (Boxes H and K of flow diagram Figure 6). 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, he/she should not receive additional investigational product; even if a sympathetic autonomic neuropathy has not been confirmed (Boxes J and L of flow diagram Figure 6), and will enter the Early Termination Follow-up Period (refer to Section 6.9). Subjects found to have a sympathetic autonomic neuropathy (Boxes I and L of flow diagram Figure 6), should not receive additional investigational product and will enter the Early Termination Follow-up Period (see Section 6.9).

Figure 6. Follow-up Procedures for Confirmed Orthostatic Hypotension Events



OH=Orthostatic Hypotension

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

On a weekly basis beginning at the IPAP 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 (e.g., 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 Sections 7.4.5 and 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 joint safety event (rapidly progressive osteoarthritis [type-1 or type-2]), subchondral insufficiency fractures (spontaneous osteonecrosis of the knee [SPONK]), primary osteonecrosis, or pathological

fracture will be withdrawn from treatment and enter the Early Termination Follow-up period (see Section 6.9).

The Central Reader will review the radiology images on an ongoing basis and provide assessments to the investigator and Pfizer. For subjects who are identified with a possible or probable event described above and for subjects undergoing total joint replacement for any reason, all images and other source documentation will be provided to the blinded tanezumab Adjudication Committee for review and adjudication of the event. The Adjudication Committee's assessment of the event will represent the final classification of the event (refer to Appendix 14).

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 6.9).

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 treatment. Follow-up procedures for these subjects are described in Section 6.9.2. The follow-up will be conducted as part of a substudy (Refer to Appendix 18) if the total joint replacement occurs before the last subject enrolled in Study A4091063 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 at Baseline (Day 1; pre-dose) and at Weeks 2 and 4, Week 8 (pre-dose), Week 16 (pre-dose), Week 32 (pre-dose), Week 48 (pre-dose), Week 56, and Week 64. If subjects terminate 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 6.9, 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, Week 8 (pre-dose), Week 48 (pre-dose) and at Weeks 56 and 64 (or at Early Termination, as described in Section 6.9). 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 6.9).

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 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]

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.

Biomarker 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 deoxyribonucleic acid (DNA),

ribonucleic acid (RNA), protein, and metabolite variation patterns of subjects who respond well and those who respond poorly to treatment may help to better define the most appropriate group of subjects in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/biomarker analyses and retaining them in the Pfizer BioBank makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study.

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

To protect subjects' confidentiality, the banked biospecimens and data generated from them will be coded with the subject's study identification (ID) number. Samples will be kept in a facility accessible only by swiping a badge, Data will be stored on password-protected computer systems. The key between the code and the subject's personal identifiers will be held at the study site; the researchers using the biospecimens and data generated from them will not have access to the key nor any personally identifying information. Biospecimens will be used only for the purposes described here and in the informed consent document/subject information sheet; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored indefinitely to allow for future research on the topics described here, including research conducted during the lengthy drug development process and also postmarketing research. Subjects can withdraw their consent for the use of their biospecimens at any time by making a request to the investigator, in which event any remaining biospecimen will be destroyed; data already generated from the biospecimens will continue to be stored to protect the integrity of existing analyses. It is very unlikely that results generated from the biospecimens will have any clinical, diagnostic, or therapeutic implications for the individual study participants. Subjects are notified in the informed consent document/subject information sheet that their results will not be given to them, 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 edetic acid [ethylenediaminetetraacetic acid] [EDTA] whole blood collection optimized for DNA analysis)** will be collected at the Baseline visit to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. For example, putative safety biomarkers, drug-metabolizing enzyme genes, drug-transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.

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

It is possible that the use of these biospecimens may result in commercially viable products. Subjects will be advised in the informed consent document/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 subjects.[28] 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 subjects. The painDETECT questionnaire will be administered at Baseline. Refer to Appendix 13 for the painDETECT questionnaire.

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

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

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

- Drug overdose;
- Drug withdrawal;

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

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the AE page, and on the serious adverse event (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 the 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 values ≥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 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 AE 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 laboratory abnormality);
- Social admission (eg, subject has no place to sleep);

- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical 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 AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the adverse event.

8.8. Severity Assessment

If required on the adverse event 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 AE. 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 event reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see the section on

8.14 Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

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

8.10. Exposure During Pregnancy

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

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

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

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

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

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless 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 Postnatal 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 AE 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 AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

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

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This 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 or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the 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 AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.14.2. Non-Serious Adverse Event Reporting Requirements

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

8.14.3. Medical Device Complaint 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.

The efficacy and safety population will be the ITT population, defined as all randomized subjects who received SC investigational product (either tanezumab or matching placebo).

9.1. Sample Size Determination

In terms of the study feasibility and the safety evaluation described below, the total sample size will be approximately 200 subjects (170-220 subjects, approximately 66 subjects [56-73 subjects] per treatment group). However, it is acceptable to randomize more than 220 subjects from the safety perspective as described below because primary objective is to evaluate the long-term safety.

Japanese subjects are enrolled in two studies within the tanezumab CLBP program (A4091059 and this study). In ongoing A4091059 study (randomization was finished in June 2017), 129 Japanese subjects were randomized and appropriately 57 Japanese CLBP subjects are expected to be initially randomized to the tanezumab arm. Considering approximately 133 (113-146) subjects are expected to be randomized to the tanezumab arm in this study, the safety data will be collected from approximately 190 (170-203) Japanese CLBP subjects treated with tanezumab.

The primary objective of this study is the evaluation of long term safety. The number of subjects who complete this study is estimated as described below. Both these protocols

require subjects to meet the efficacy response criteria (defined as at least a 30% reduction in weekly average LBPI score at week 16 relative to Baseline and at least a 15% reduction in weekly average LBPI score from Baseline at any week from week 1 to week 15) at week 16 in order to continue in the study. The proportion of 30% responders at week 16 was approximately 60% in two OA phase 3 studies (A4091011, A4091014) and approximately 42% in one CLBP phase 3 study (A4091012). On the other hand, the proportion of subejcts discontinuing after week 16 is assumed to be approximately 10% for OA and approximately 20% for CLBP based on the results of discontinuation for reasons other than insufficient clinical response in these studies.

Therefore, the proportion of subjects expected to complete this study was calculated as approximately 54% (=100*0.6*0.9) based on the two OA studies and approximately 34% (=100*0.42*0.8) based on the CLBP study, and the proportion of completers of this study is estimated to be between 34% and 54%. Table 6 shows the relationship between the proportion of completers and the number of subjects with one year exposure.

From Table 6, if the proportion of completers is at least 43% in the CLBP program, approaching 100 subjects are expected to be treated with tanezumab for a minimum of one year.

Table 6. The relationship between the proportion of completer and number of subjects with one year exposure

Proportion of completers	Tanezumab treated Japanese sample size with 1 year of treatment exposure	
	CLBP program total	A4091063 only
54 %	91-109	61-78
50 %	85-101	56-73
45 %	76-91	50-65
43 %	73-87	48-62
40 %	68-81	45-58
34 %	57-69	38-49

(randomized 170 subjects in this study – randomized 220 subjects in this study)

As described below, when approximately 200 (170-220) Japanese subjects are enrolled in this study, the adverse events related to abnormal peripheral sensation and decreased sympathetic function are expected to occur in several Japanese subjects, so neurological safety can be evaluated with high probability in Japanese subjects.

Adverse events related to abnormal peripheral sensation[1]

The incidence of adverse events related to abnormal peripheral sensation was 8.6% in the tanezumab 5 mg group and 15.6% in 10 mg group of the phase II controlled study of

[1] Details are described in section 7.3.9.

tanezumab conducted in CLBP subjects (A4091012). Also, the incidence was 15.6% in 10 mg group of the phase II uncontrolled study (A4091039). Assuming that the true incidence rate of these events in the subjects enrolled in A4091059 and this study is nearly equal (10% in tanezumab treated subjects), when 170 subjects are enrolled in this study (approximately 113 subjects will be treated with tanezumab), these adverse events are expected to occur in 7 to 15 subjects (6%-13%) in this study at a probability of ≥80%, and in 12 to 22 subjects (7%-13%) in combined A4091059 and this study (approximately 170 subjects will be treated with tanezumab) at a probability of ≥80%.

Adverse events related to decreased sympathetic function [2]

The incidence of adverse events related to decreased sympathetic function was 6.0% in the tanezumab 5 mg group and 5.1% in 10 mg group of the phase II controlled study of tanezumab conducted in CLBP subjects (A4091012). Also, the incidence was 4.1% in 10 mg group of the phase II uncontrolled study (A4091039). Assuming that the true incidence rate of these events in the subjects enrolled in A4091059 and this study is nearly equal (6% in tanezumab treated subjects), when 170 subjects are enrolled in this study, these adverse events are expected to occur in 4 to 10 subjects (4%-9%) in this study at a probability of ≥80%, and in 6 to 14 subjects (4%-8%) in combined A4091059 and this study at a probability of ≥80%.

9.2. 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 and the celecoxib group, together with 95% confidence interval, using exact methods.

- 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

[2] Details are described in section 9.2.

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 E-DMC (See Section 9.6).

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

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

- The NIS is the sum of scores over all 37 items from both the Left and Right side. The change from baseline to each post-baseline visit in the NIS will be summarized. The change from Baseline to each study visit, 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). 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 subject years of exposure (treatment plus follow-up periods), for individual treatment groups and differences between tanezumab treatment groups and the celecoxib treatment group. The risk ratio and risk difference with 95% Confidence intervals will be calculated for the comparisons of each tanezumab group versus the celecoxib group. 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.

- 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 ADA impact on the individual's efficacy and safety profile.

9.3. Analysis of Efficacy Endpoints

Efficacy endpoints regarding the continuos data will examine the change from Baseline to each timepoints (Week 2, 4, 8, 12 [LBPI score only], 16, 24, 32, 40, 48, 56 and 64) in LBPI score, RMDQ total score, Patient Global Assessment of Low back Pain and BPI-sf measures. The differences with 95% confidence intervals will be calculated for the comparisons of each tanezumab group versus the celecoxib group. Detailes for the missing handling will be documented in the Statiltical Analysis Plan.

Subject response endpoints of improvement in the average LBPI 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 summarized to Weeks 16, 24, 40 and 56. The differences with 95% confidence intervals will be calculated for the comparisons of each tanezumab group versus the celecoxib group. Detailes for the missing handling will be documented in the Statiltical Analysis Plan. Cumulative average LBPI response at Week 16, 24 and 56 using response definitions from a reduction of >0% to =100% (in steps of 10%) will be summarized.

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 16 and 56. 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 Week 16, 56 and 64 or Early Termination in the WPAI:LBP impairment scores will be shown by treatment group.

All data from TSQM and mPRTI will be summarized by visit. The HCRU data will be reported as outlined in the SAP.

The incidence of and time to withdrawal due to lack of efficacy will also be summarized for discontinuations up to Week 16 and 56. Kaplan-Meier estimates of the time to discontinuation will be shown for selected percentiles, dependent on the level of discontinuation. The expectation is that these would be the 1^{st}, 2^{nd}, 5^{th}, 10^{th} and 25^{th} 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 incidence and number of days of rescue medication use will be summarized during Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, 56 and 64, and the amount of rescue medication taken in a week summarized during Weeks 2, 4, 8, 12 and 16.

For the efficacy analysis, the observed data (no imputation for missing data) will be summarized. Additional analyses may explore the sensitivity of the efficacy analysis results to missing data. The details will be provided 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.

9.4. 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.

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

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

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

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

basis. A safety review plan will be in place governing the frequency and extent of safety review.

9.6.1. Protocol Level Rules for Dosing Suspension/Safety Assessment

9.6.1.1. Serious Adverse Events

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

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

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

- Consideration of relationship of investigational product to the adverse event.
- Consideration of whether similar adverse events are occurring in other tanezumab studies with similar subject populations.
- Dosage of tanezumab (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.
- 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 E-DMC will determine whether the dosing suspension should be triggered. Subsequently the E-DMC will formulate a recommendation whether all studies should be permanently terminated. Decisions regarding permanently stopping treatment and terminating studies will be made by the Sponsor in consultation with the DMC.

9.6.1.3. Joint Safety Events

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

The protocol (or treatment group) stopping rule 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 celecoxib 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 [redacted] 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 E-DMC will formulate a recommendation whether it is safe to continue dosing in some or all treatment groups or whether the study should be terminated completely. This decision will be made by Pfizer in consultation with the E-DMC.

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

During study conduct and/or after study completion, the study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

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

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs 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 the International Conference on Harmonisation (ICH) guidelines, 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/EC. All correspondence with the IRB/EC 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 are compiled for transfer to Pfizer and other authorized parties, subject names, address, and other identifiable data will be replaced by a numerical code based on a numbering system provided by Pfizer in order to de-identify study subjects. The study site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

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

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

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

Whenever consent is obtained from a subject's legally acceptable representative, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents

must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

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

12.4. Subject Recruitment

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

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

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

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

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

13. DEFINITION OF END OF TRIAL

End of trial is defined as database lock.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product 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.

www.clinicaltrials.gov

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 prespecified protocol or was terminated.

EudraCT

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

www.pfizer.com

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

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed

publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

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

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

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

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

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

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

16. REFERENCES

1 Bennett DLH, McMahon SB, Rattray M, et al. Nerve growth factor and sensory nerve function. In:Brain SD, Moore PK editors. Pain and Neurogenic Inflammation. Basel: Birkhäuser; 1999: 167-93.

2 Woolf CJ, Safieh-Garabedian B, Ma QP, et al. Nerve growth factor contributes to the generation of inflammatory sensory hypersensitivity. Neuroscience 1994; 62(2):327-31.

3 McMahon SB, Bennett DLH, Priestley JV, et al. The biological effects of endogenous nerve growth factor on adult sensory neurons revealed by a trkA IgG fusion molecule. Nature Med 1995; 1(8):774-80.

4 Armour KL, Clark MR, Hadley AG, et al. Recombinant human IgG molecules lacking Fcgamma receptor I binding and monocyte triggering activities. Eur J Immunol 1999; 29(8):2613-24.

5 Armour KL, van de Winkel JG, Williamson LM, et al. Differential binding to human FcgammaRIIa and FcgammaRIIb receptors by human IgG wild type and mutant antibodies. Mol Immunol 2003; 40(9):585-93.

6 Borenstein D. Chronic low back pain. Musculoskeletal Medicine 1996; 22 (3);439-56.

7 Praemer A, Furnos S, Rice DP. Musculoskeletal conditions in the United States. Rosemont: AAOS; 1992: 1-99.

8 Johannes C, Le TK, Zhou X, et al. The prevalence of chronic pain in the United Stated adults: results of an internet-based survey. Journal of Pain 2010; 11(11):1230-9.

9 Airakinsinen O, Brox JI, Hildebrandt, et al. European guidelines for the management of chronic non specific low back pain. Eur Spine J 2006; 15 (Suppl. 2):S192-300.

10 Fujii T, Matsudaira K. Prevalence of low back pain and factors associated with chronic disabling pain in Japan. Eur Spine J. Published online: 07 Aug 2012.

11 Deyo RA, Weinstein JN. Low back pain. N Engl J Med 2001; 344(5):363-70.

12 Pfizer Data on File A4091004 CSR approved 8 July 2009.

13 Pfizer Data on File A4091012 CSR approved 21 Dec 2011.

14 Pfizer Data on File A4091039 CSR approved 11 May 2012.

15 Pfizer Data on File A4091027 CSR approved 01 Feb 2012.

16 Pfizer Data on File A4091043 CSR approved 03 Feb 2011.

17 Pfizer. TANEZUMAB ARTHRITIS ADVISORY COMMITTEE BRIEFING DOCUMENT. February 8, 2012; In 2012. URL: http://www.fda.gov/AdvisoryCommittees/Calendar/ucm286556.htm?utm_source=fdaSearch&utm_medium=website&utm_term=March 12, 2012&utm_content=1. Access Date: April 4, 2012.

18 Pfizer Data on File A4091013 CSR approved 22 Mar 2010.

19 Pfizer Data on File A4091022 CSR approved 7 July 2010.

20 Spitzer RL, Kroenke K, Williams J. Validation and utility of a self-report version of PRIME-MD. JAMA 1999; 282(18):1737-44.

21 Roland M, Fairbank. The Roland-Morris Questionnaire and the Oswestry Disability Questionnaire. Spine. 2000; 25(4)3115-24.

22 Reilly MC, Zbrozek AS, Dukes, EM. The validity and reproducibility of a work productivity and activity impairment instrument. PharmacoEconomics 1993; 4(5):353-65.

23 Devlin NJ, Krabbe PF. The development of new research methods for the valuation of EQ-5D-5L. Eur J Health Econ 2013; 14 Suppl 1:S1-3.

24 Atkinson MJ, Kumar R, Cappellari JC, et al. Hierarchical Construct Validity of the Treatment Satisfaction Questionnaire for Medication (TSQM Version II) Among Outpatient Pharmacy Consumers. Value in Health 2005; 8 Suppl 1:S9-24.

25 Okkalides D, Fotakis M. Patient effective dose resulting from radiographic examinations. Br J Radiol. 1994; 67(798):564-72.

26 Huda W, Gkanatsios NA. Radiation dosimetry for extremity radiographs. Health Phys. 1998; 75(5):492-9.

27 Dyck PJ, Litchy WJ, Lehman KA, Hokanson JL, Low PA, and O'Brien PC. Variables influencing neuropathic endpoints: The Rochester Diabetic Neuropathy Study of Healthy Subjects. Neurology 1995; 45(6):1115-21.

28 Freynhagen R, BaronR, Gockel U, and Tolle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin 2006; 22(10):1911-20.

29 Altman R, Asch E, Bloch D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the knee. Arthritis Rheum 1986; 29(8):1039-49.

30 Dripps RD. New classification of physical status. Anesthesiol 1963; 24:111.

Abbreviations

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

Abbreviation	Term
ACR	American College of Rheumatology
ADA	Anti-drug antibody
AE	Adverse event
AEMPS	Agency on Medicinal Products and Medical Devices
ALT	Alanine aminotransferase
ASA	American Society of Anesthesiologists
AST	Aspartate aminotransferase
AUC	Area under the concentration -time curve
AUC_{inf}	Area under the concentration -time curve from time zero to infinity
BID	Twice a day
BMI	Body mass index
BOCF	Baseline observation carried forward
BP	Blood pressure
BPI	Brief Pain Inventory
BUN	Blood urea nitrogen
CCI	[redacted]
CDS	Core data sheets
CI	Confidence interval
CLBP	Chronic low back pain
C_{max}	Maximum observed concentration
COX-2	Cyclooxygenase 2
CPK	Creatine phosphokinase
CRF	Case report form
CRA	Clinical Research Associate
CCI	[redacted]
CSA	Clinical study agreement
CTS	Carpal tunnel syndrome
CCI	[redacted]
CYP	Cytochrome
DAI	Dosage and administration instructions
DNA	Deoxyribonucleic acid
EC	Ethics committee
ECG	Electrocardiogram

Abbreviation	Term
E-DMC	External Data Monitoring Committee
EDP	Exposure during pregnancy
EDTA	Edetic acid (ethylenediaminetetraacetic acid)
E_{max}	Maximum observed pharmacodynamic effect
EQ-5D-5L	EuroQol 5 Dimension
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
Hb	Hemoglobin
CCI	
HCRU	Health Care Resources Utilization
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
CCI	
HR	Heart rate
IB	Investigator's brochure
ICH	International Conference on Harmonisation
ICRP	International Commission on Radiation Protection
CCI	
ID	Identification
IND	Investigational New Drug application
INR	International Normalized Ratio
IgG	Immunoglobulin G
IgG2	Immunoglobulin G Type 2
IRB	Institutional review board
CCI	
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

Abbreviation	Term
LOCF	Last observation carried forward
MHLW	Ministry of Health, Labour and Welfare
MHRA	United Kingdom's Medicines and Healthcare products Regulatory Agency
CCI	
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
CCI	
OTC	Over-the-counter
PD	Pharmacodynamic
PEI	Paul Ehrlich Institute
PHQ-9	Patient Health Questionnaire-9
PFS	Pre-filled syringe
PGA	Patient Global Assessment
CCI	
PK	Pharmacokinetic
PPK	Population pharmacokinetics
PT	Prothrombin 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

Abbreviation	Term
RA	Rheumatoid Arthritis
RMDQ	Roland-Morris Disability Questionnaire
RNA	Ribonucleic acid
RD	Risk difference
RR	Risk ratio
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Survey of Autonomic Symptoms
SC	Subcutaneous
CCI	
SPONK	Spontaneous osteonecrosis of the knee
SRSD	Single reference safety document
T_{max}	Time to first occurrence of C_{max}
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
V_{ss}	Steady-state volume of distribution
WOMAC	Western Ontario and McMaster University Osteoarthritis Index
WPAI:LBP	Work Productivity and Activity Impairment Questionnaire: Low Back Pain

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[29]

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[29]

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;[30] a sixth category was later added. These are:

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

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

NSAIDs and Other Analgesics

Use of analgesics except acetaminophen/paracetamol is prohibited through Week 64 of the study beginning 48 hours prior to the start of the IPAP (the 5 days prior to Randomization/Baseline (Day 1) or at the period of time prior to the start of the IPAP that is at least 5 times the half-life of the particular analgesic used, whichever is greater. Note that a stable regimen of aspirin taken for cardiac prophylaxis at a dose of ≤324 mg/day is permitted throughout the study.

These lists are not all-inclusive and include unapproved medications in Japan. The Physician's Desk Reference provides half-life information.

HALF-LIVES OF NSAIDs AND OTHER ANALGESICS		
Analgesic	**Half-life (hours)**	**Minimum Washout Period**
Aspirin >324 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
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
Meperidine	3.7	2 days
Mexiletine	6.0-17.0	4 days

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

Muscle Relaxants

Use of any muscle relaxants is prohibited during the Treatment Period up to Week 16 beginning 48 hours prior to the start of the IPAP (the 5 days prior to Randomization/Baseline) or at the period of time prior to the start of the IPAP that is 5 times the half-life of the particular muscle relaxant used, whichever is greater.

Subjects who have taken a stable dose of the particular muscle relaxants for at least 30 days prior to Screening will be allowed to continue their regimen.

These lists are not all-inclusive and include unapproved medications in Japan. 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
Flupirtine	7.0-10.0	3 days
Meprobamate	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

All anti-depressants for the treatment of depression are prohibited beginning within 30 days prior to Screening.

Anti-depressants prescribed for the treatment of chronic low back pain are prohibited beginning 48 hours to start of the IPAP or at the period of time prior to the start of the IPAP that is 5 times the half-life of the particular anti-depressants used, whichever is greater.

Subjects who are anticipated to need to initiate treatment with an antidepressant from Baseline to Week 16 should not be enrolled.

Subjects who have taken a stable dose of the anti depressants for the treatment of depression and low back pain for at least 30 days prior to Screening will be allowed to continue their regimen.

These lists are not all-inclusive and include unapproved medications in Japan. The Physician's Desk Reference provides half-life information.

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
Ttrimipramine	Moclobemide
Monoamine Oxidase Inhibitors (MAOIs)	**Miscellaneous Antidepressants**
Phenelzine	Bupropion
Selegiline	Mirtazapine
Tranylcypromine	St John's Wort
	Trazodone
Selective Serotonin Reuptake Inhibitors (SSRIs)	
Citalopram	Escitalopram
Fluoxetine	Fluvoxamine
Paroxetine	Sertraline

Centrally Acting Agents

Other centrally acting agents are allowed with limitations. The use of any sedatives/hypnotics, anxiolytics, tranquilizers, or benzodiazepines are prohibited beginning within 30 days prior to the Screening. Benzodiazepines prescribed as a muscle relaxant are prohibited and must be discontinued via washout. In this case, refer to Muscle Relaxants.

Subjects who have taken a stable dose of the centrally acting agents for at least 30 days prior to Screening will be allowed to continue their regimen.

These lists are not all-inclusive and include unapproved medications in Japan. The Physician's Desk Reference provides half-life information.

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 IPAP 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 [these vaccines are not approved in Japan]) is prohibited within 3 months of IPAP and during the study.

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

Live attenuated vaccines	
Generic	**Brand**
BCG (for tuberculosis)	Not available in the US
Herpes zoster vaccine	Zostavax
Influenza, intranasal	FluMist
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)

PATIENT HEALTH QUESTIONNAIRE (PHQ-9):

Over the last 2 weeks, 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**
☐	☐	☐	☐

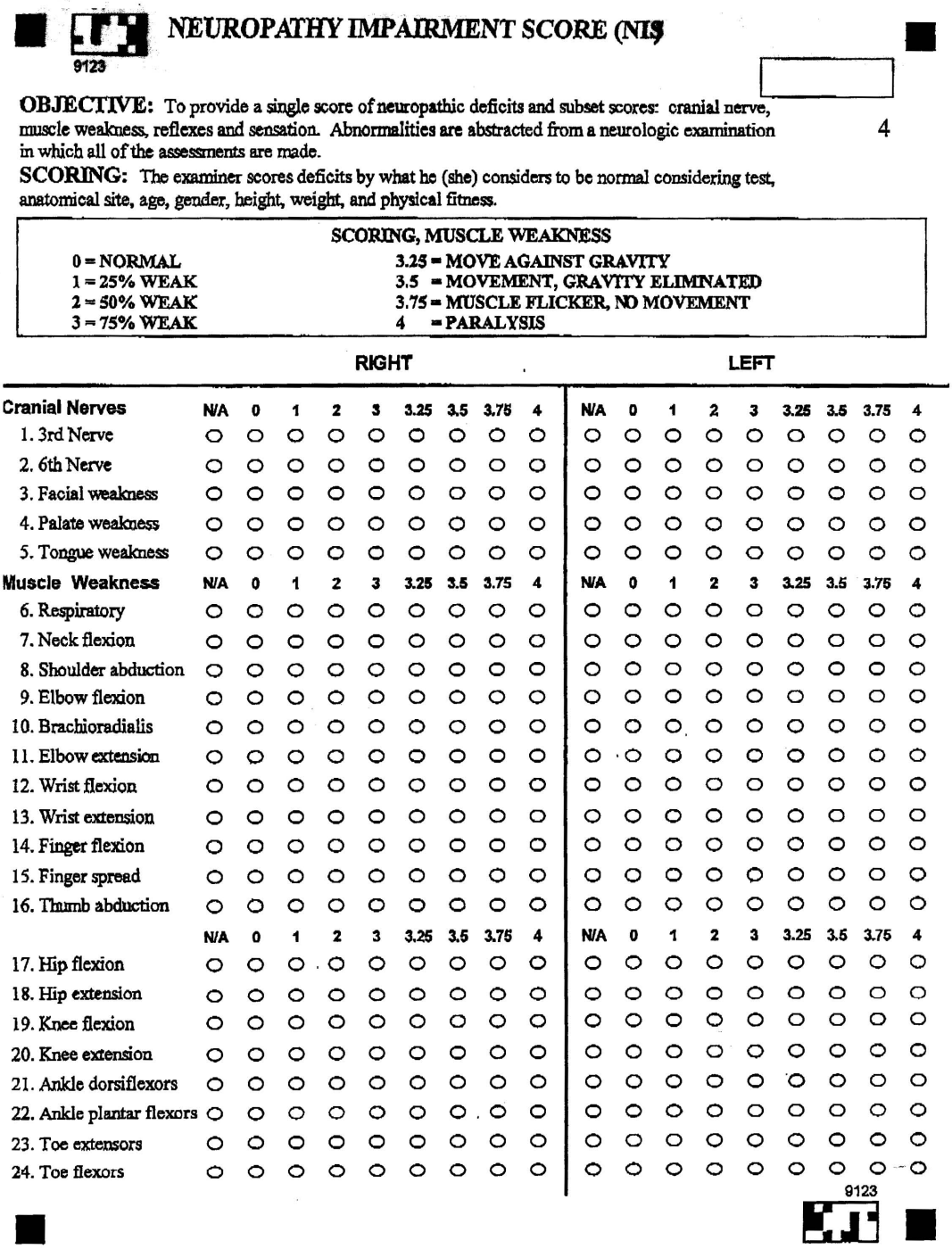
Appendix 6. Roland-Morris Disability Questionnaire (RMDQ)

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. Neuropathy Impairment Score (NIS) Sample



NEUROPATHY IMPAIRMENT SCORE (NIS)

9123

OBJECTIVE: To provide a single score of neuropathic deficits and subset scores: cranial nerve, muscle weakness, reflexes and sensation. Abnormalities are abstracted from a neurologic examination in which all of the assessments are made.

SCORING: The examiner scores deficits by what he (she) considers to be normal considering test, anatomical site, age, gender, height, weight, and physical fitness.

4

SCORING, MUSCLE WEAKNESS

0 = NORMAL	3.25 = MOVE AGAINST GRAVITY
1 = 25% WEAK	3.5 = MOVEMENT, GRAVITY ELIMNATED
2 = 50% WEAK	3.75 = MUSCLE FLICKER, NO MOVEMENT
3 = 75% WEAK	4 = PARALYSIS

	RIGHT									LEFT								
Cranial Nerves	N/A	0	1	2	3	3.25	3.5	3.75	4	N/A	0	1	2	3	3.25	3.5	3.75	4
1. 3rd Nerve	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
2. 6th Nerve	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
3. Facial weakness	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
4. Palate weakness	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
5. Tongue weakness	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Muscle Weakness	N/A	0	1	2	3	3.25	3.5	3.75	4	N/A	0	1	2	3	3.25	3.5	3.75	4
6. Respiratory	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
7. Neck flexion	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
8. Shoulder abduction	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
9. Elbow flexion	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
10. Brachioradialis	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
11. Elbow extension	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
12. Wrist flexion	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
13. Wrist extension	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
14. Finger flexion	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
15. Finger spread	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
16. Thumb abduction	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	N/A	0	1	2	3	3.25	3.5	3.75	4	N/A	0	1	2	3	3.25	3.5	3.75	4
17. Hip flexion	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
18. Hip extension	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
19. Knee flexion	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
20. Knee extension	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
21. Ankle dorsiflexors	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
22. Ankle plantar flexors	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
23. Toe extensors	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
24. Toe flexors	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○

9123

NEUROPATHY IMPAIRMENT SCORE (NIS)

9123

5

For patients 50-69 years old, ankle reflexes which are decreased are graded 0 and when absent are graded 1.
For patients ≥ 70 years, absent ankle reflexes are graded 0.

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

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

Touch-pressure, pin-prick and vibration sensation are tested on the dorsal surface, at the base of the nail, of the terminal phalanx of the index finger and great toe. Touch-pressure is assessed with long fiber cotton wool. Pin-prick is assessed with straight pins. Vibration sensation is tested with a 165 hz tuning fork (V. Mueller, Chicago, length 25 cm, made from 1/2" x 1 1/4 " stock; 165 hz with counterweights). Joint motion is tested by moving the terminal phalanx of the index finger and great toe.

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

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

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Appendix 8. 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


CCI


CCI

Appendix 10. 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												LOW BACK PAIN completely prevented me from working
	0	1	2	3	4	5	6	7	8	9	10	

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 11. Subject Daily/Weekly Assessments of Low Back Pain

Daily and Weekly Assessments

Subjects will use IRT to complete questionnaires recording subject average daily low back pain intensity (LBPI) scores with a 24-hour recall. The LBPI score will be captured once daily during the Initial Pain Assessment Period, and weekly from Baseline through to Week 64 or Early Termination Visit 2, in the evening if possible.

Low Back Pain Intensity (from the beginning of the Initial Pain Assessment Period to Week 64 or Early Termination Visit 2):

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 12. 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.

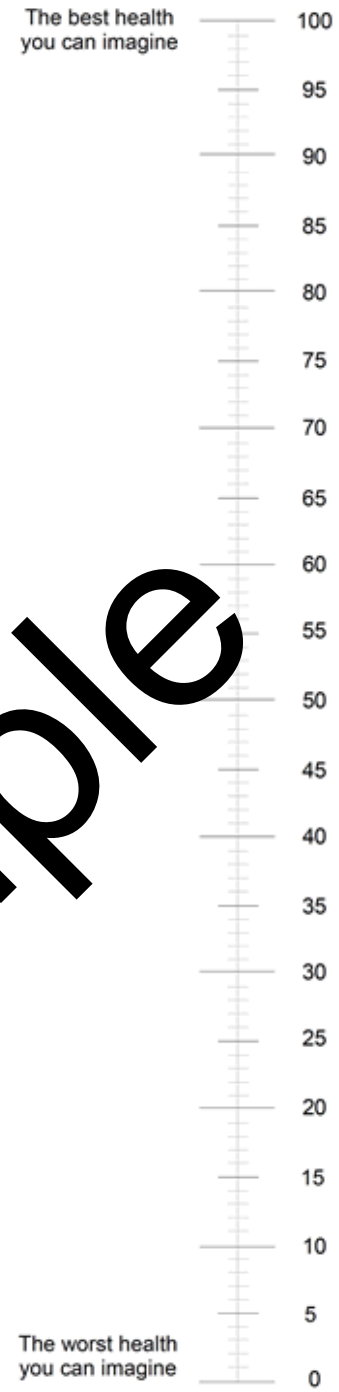
This scale is numbered from 0 to 100.

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.

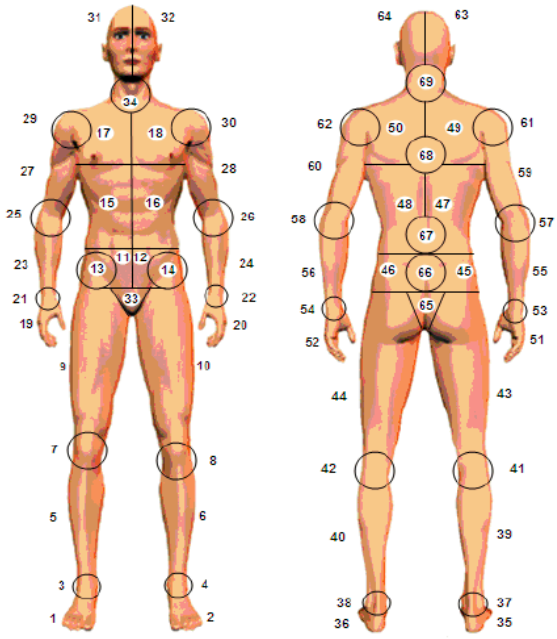


Health State: ___

Appendix 13. 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 14. 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 15. Survey of Autonomic Symptoms (SAS)

Table 1 Survey of Autonomic Symptoms[a]

	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)
Symptom/health problem		
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

[a] 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 16. 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 17. 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 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 A4091063 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 A4091063 (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 A4091063 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 A4091063 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 A4091063.

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 A4091063). 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 7) 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 7. 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 A4091063 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 A4091063 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 A4091063 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 StudyA4091063 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 A4091063.
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 A4091063 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 StudyA4091063. 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 A4091063 (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 by the 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 A4091063 (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 A4091063 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 A4091063 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 A4091063. 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 A4091063 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 A4091063. Subjects undergoing total knee, hip or shoulder replacement surgery after the last subject completes the treatment period in Study A4091063 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 A4091063 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 A4091063 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 A4091063 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 A4091063 protocol).

105. SUBSTUDY STUDY TREATMENTS

This is an observational study of subjects who were randomized and treated in tanezumab Study A4091063 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 A4091063.

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 A4091063 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 A4091063 (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 A4091063, 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 A4091063, 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 A4091063, 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 A4091063, 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 A4091063, 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:

4. Uneventful; or

5. Minor complications; or

6. 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 A4091063 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 assessment.

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).

Question:

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 A4091063 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 A4091063. 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 A4091063).

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 A4091063 protocol.

109.4. External Adjudication Committee

Refer to Section 9.5 of the A4091063 protocol.

110. SUBSTUDY QUALITY CONTROL AND QUALITY ASSURANCE

Refer to Section 10 of the A4091063 protocol.

111. SUBSTUDY DATA HANDLING AND RECORD KEEPING

Refer to Section 11 of the A4091063 protocol.

112. SUBSTUDY ETHICS

Refer to Section 12 of the A4091063 protocol.

113. SUBSTUDY DEFINITION OF END OF TRIAL

Refer to Section 13 of the A4091063 protocol.

114. SUBSTUDY SPONSOR DISCONTINUATION CRITERIA

Refer to Section 14 of the A4091063 protocol.

115. SUBSTUDY PUBLICATION OF STUDY RESULTS

Refer to Section 15 of the A4091063 protocol.

116. SUBSTUDY REFERENCES

a. Beaton DE, and Schemitsch E. Measures of Health-Related Quality of Life and Physical Function. Clin Orth and Rel Research 413:2003; 90-105.

b. Mahomed N, et al. The self-administered patient satisfaction scale for primary hip and knee arthroplasty. Arthritis 2011; doi:10.1155/2011/591253.

c. Hawker GA, et al. Measures of adult pain. Arthritis Care Res 2011;63:S240-52.

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.

e. Beaton DE and Schemitsch E. Measures of health-related quality of life and physical function. Clin Orth Rel Res 2003; 413:90-105.

f. Rogers JC and Irrgang JJ. Measures of adult lower extremity function. Arthritis Care Res 2003;49:S67-84.

g. Angst F, et al. Measures of adult shoulder function. Arthritis Care Res 2011;63:S174-88.

h. Roy J-S, MacDermid JC and Woodhouse LJ. Measuring shoulder function: a systemic review of four questionnaires. Arthritis Care Res 2009; 61:623-32.

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; 2279-92.

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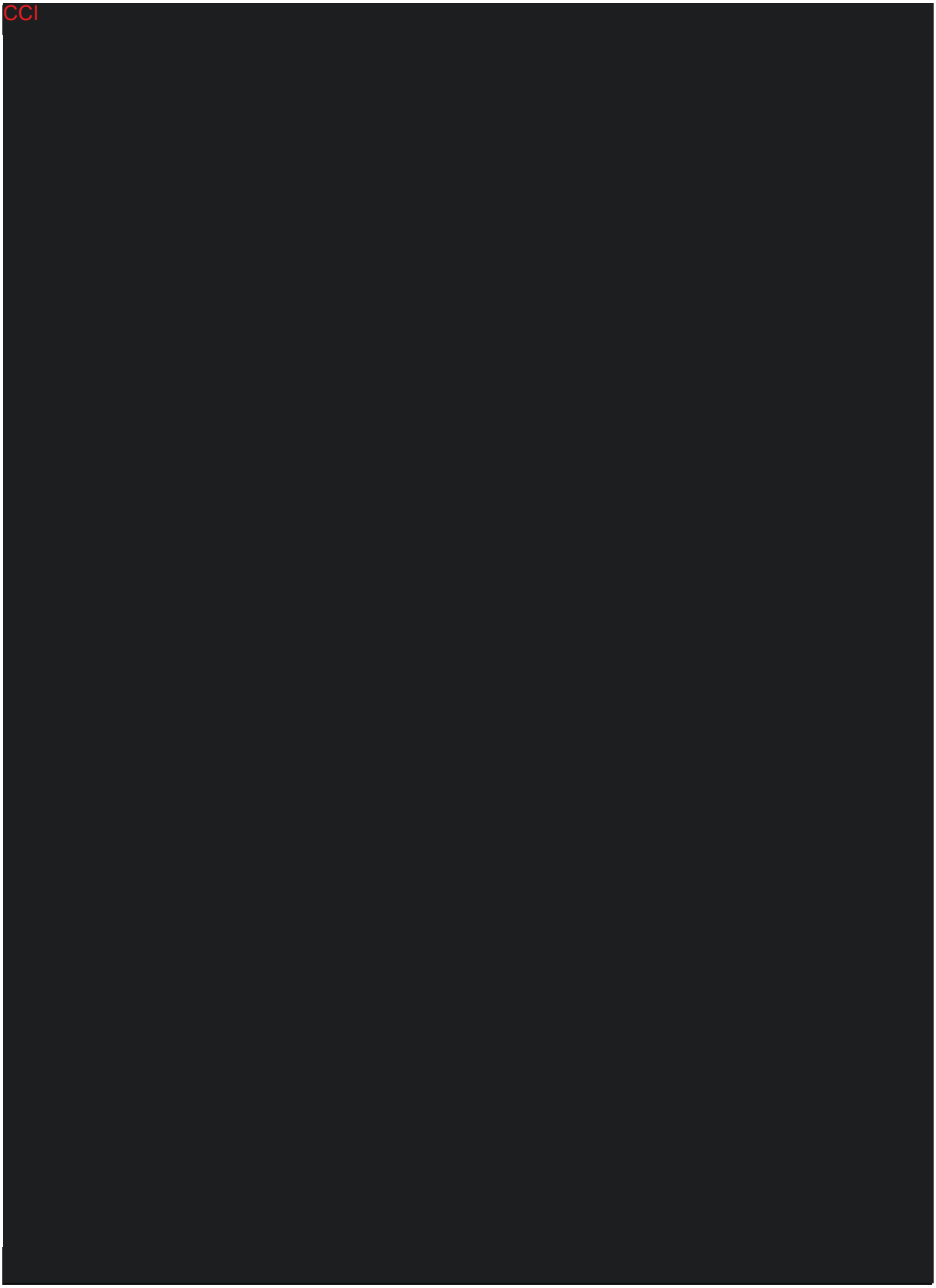
[redacted]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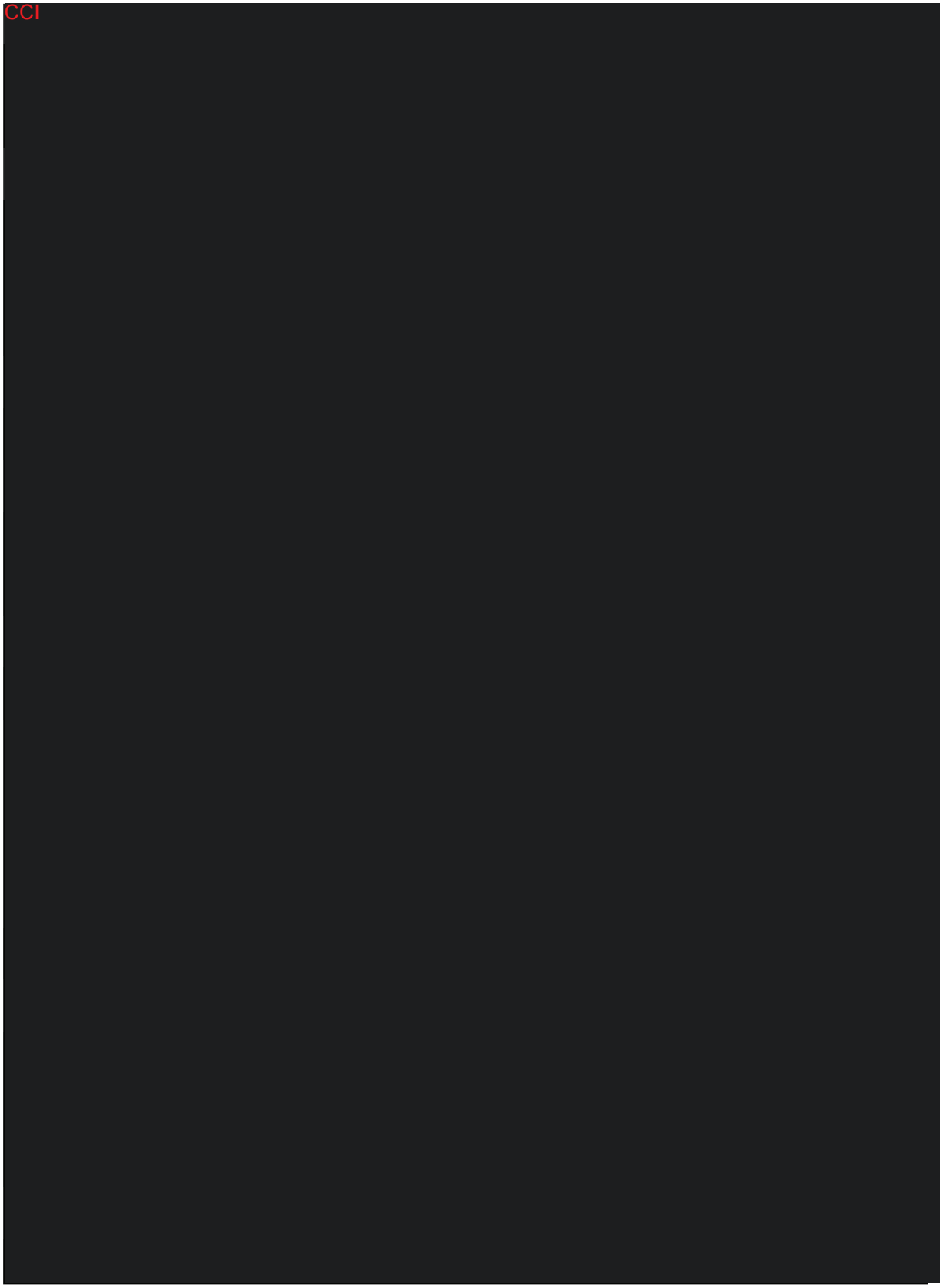
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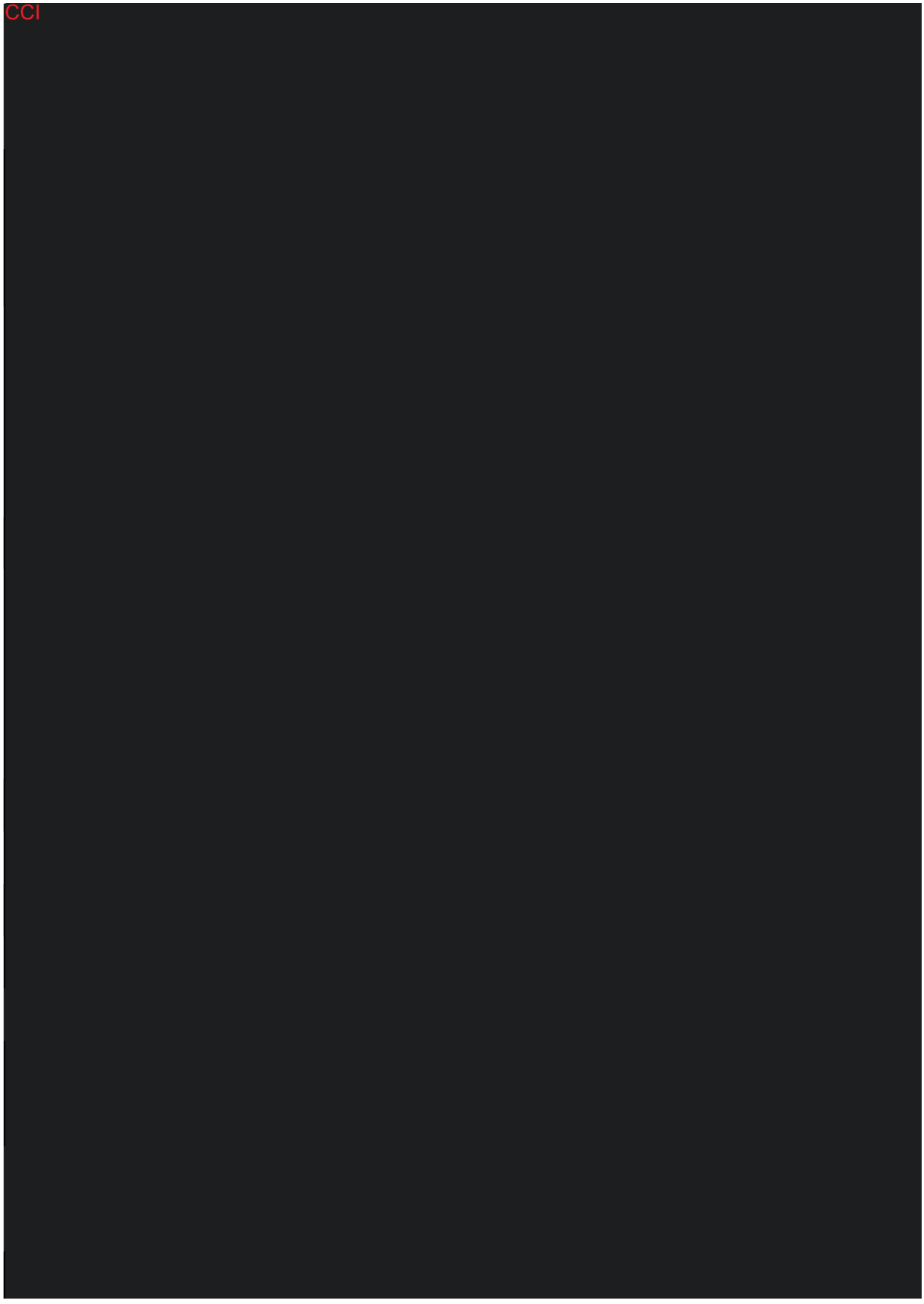
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Appendix 20. The Shoulder Pain and Disability Index (SPADI)

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