CLINICAL PROTOCOL

A PHASE 3, MULTICENTER, LONG-TERM OBSERVATIONAL STUDY OF SUBJECTS FROM TANEZUMAB STUDIES WHO UNDERGO A TOTAL KNEE, HIP OR SHOULDER REPLACEMENT

Compound:	PF-04383119
Compound Name:	Tanezumab
United States (US) Investigational New Drug (IND):	BB-IND 11,680
European Clinical Trial Database (EudraCT) Number:	2013-002549-12
Protocol Number:	A4091064
Phase:	Phase 3

Document History

Document	Version Date	Summary of Changes
Sweden and United Kingdom Specific - Amendment 1	06 January 2016	• Section 1.2.6: Summary of Benefits and Risks to Subjects enrolled in Study A4091064 added. • Section 4.2: Reference to Appendix 4 added. • Section 12.1: Institutional Review Board/Ethics Committee updated to add that investigator should also receive approval from the national competent authority before implementing a substantial amendment. • Appendix 4: Life Style Guidelines for subjects from sites in Sweden and the United Kingdom added.
Original Protocol	01 April 2015	Not Applicable (N/A)

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

PROTOCOL SUMMARY

Background

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

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

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

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

Measures to better characterize the joint safety issue have been developed and agreed with FDA. This study is 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 study and the duration of the study have been agreed to with the FDA.

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

In animal studies in rats and non-human primates, tanezumab treatment for up to 6 months, with doses producing greater systemic exposure than observed with clinical doses, was associated with lower sympathetic ganglion volume and lower average size of

post-ganglionic sympathetic neurons when compared to control animals. All effects were completely reversible following a dosing-free recovery period. In a separate cardiovascular function study in non-human primates, functional changes in the cardiovascular system controlled by the sympathetic nervous system were not observed. In March 2015, the FDA lifted the partial clinical hold on tanezumab allowing the resumption of clinical studies for osteoarthritis, chronic low back pain, and all other chronic pain conditions.

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

Study Objectives and Endpoints

Primary Objective:

- To describe the post-operative outcome of subjects who underwent a total knee, hip, or shoulder replacement while participating in tanezumab Study A4091056, A4091057 or A4091058 (treatment period and safety follow-up period).

Secondary Objectives:

- To compare the post-operative outcome for tanezumab 2.5 mg and 5 mg versus non-steroid anti-inflammatory drugs (NSAIDs) for subjects who underwent a total knee, hip, or shoulder replacement while participating in tanezumab Study A4091058.

- To describe the post-operative outcome of subjects from tanezumab Study A4091059, A4091061 or A4091063 who underwent a total knee, hip, or shoulder replacement

Endpoints:

The following endpoints are considered co-equal:

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

- Subject'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; see also Section 9).

- 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 Western Ontario and McMaster Universities Osteoarthritis Index (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 Shoulder Pain and Disability Index (SPADI) in the replaced shoulder (subjects undergoing total shoulder replacement surgery only).

- Concomitant analgesic medication use.

Study Design

This is a Phase 3, multicenter, long-term observational study of subjects from tanezumab Study A4091056, A4091057 or A4091058 (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 study (A4091064), 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 in the study completes the treatment period in tanezumab studies A4091059, A4091061 or A4091063 may be followed in this study (A4091064).

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

All events of total knee, hip or shoulder replacement will be reviewed by the Joint Safety Adjudication Committee (Adjudication Committee) established for the tanezumab clinical program.

Statistical Methods

This study 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 A4091056, A4091057 or A4091058. In addition subjects with a qualifying total joint replacement after the last subject in the study completes the treatment period in studies A4091059, A4091061 or A4091063 may be included. The number of subjects who will enroll in this study is unknown but is estimated to be less than 250 subjects. Also unknown is the distribution of subjects across treatment groups (ie, the treatment given in Study A4091056, A4091057, A4091058, or other tanezumab study). Therefore, it is predicted that there will be insufficient statistical power to perform statistical inferential analyses. All analyses will be descriptive in nature.

All subjects enrolled in the study who have a total joint replacement will be included in the summary tables.

A summary of data will be shown using subjects from study A4091058. The incidence of subjects with a total joint replacement will be summarized for all subjects, and split by Study A4091058 treatment group. Comparisons of the total joint replacement rates will be made between tanezumab versus active comparator treatment groups, using risk differences and ratios with 95% confidence intervals. Summaries of the time to total joint replacement surgery and time to first symptom (leading to total joint replacement surgery) will be summarized using Kaplan-Meier survival estimates from the date of first subcutaneous dose in Study A4091058, and shown overall, and split by Study A4091058 treatment group where there are sufficient numbers of subjects. A further summary of the incidence of subjects with total joint replacements will be shown separately for studies A4091056, A4091057, A4091059, A4091061 and A4091063, as applicable. Similar summaries by study will be shown for adjudication outcomes. The summary of time to total joint replacement surgery and time to first symptom (leading to total joint replacement surgery) will also be performed using data for subjects from Studies A4091056 and A4091057.

Unless otherwise stated, data from this study will be presented at Baseline and Weeks 4, 12, and 24 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 when Baseline data are available and where relevant. Data will be shown overall, and split by treatment group. Data on surgical difficulty and outcomes, and subject safety data will be summarized by study, with an additional combined summary for the subjects from the osteoarthritis studies.

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 will be stratified by surgery type (hip, knee or shoulder) and summarized for each of the four items. The total

score will be stratified by surgery type (hip, knee or shoulder) and summarized. Reponses to the question "How satisfied are you with the results of your surgery?" will also be stratified by surgery type (hip, knee or shoulder) and 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 (Numeric Rating Scale, 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 Baseline summaries).

Standard safety reporting tables will summarize and list adverse event and concomitant analgesic medications data.

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 will be used for guidance in developing the list of post-surgical complications. The list of post-surgical complications will be developed during Study A4091064 and finalized prior to Study A4091058 database lock.

Separate adverse event summaries by parent study treatment group for adverse events of decreased sympathetic function will be presented.

For subjects from study A4091058 and for subjects from any of the osteoarthritis studies, summaries of total joint replacement, adjudication event rates and post-surgical outcomes will be shown for subgroups including age, gender, body-mass index (BMI), baseline Kellgren-Lawrence grade of the replaced joint (knees and hips only) and number of joints with osteoarthritis (OA).

Data Monitoring Committee

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

SCHEDULE OF ACTIVITIES

The Schedule of Activities table (Table 1) provides an overview of the protocol visits and procedures. Refer to STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

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

Table 1. SCHEDULE OF ACTIVITIES

Study Activities			**Post-Surgery**					
Visit Identifier	**Baseline[a]**	**Day 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24/ET**
	Last visit in Study A4091056, A4091057 or A4091058[b] or when notified of TJR surgery	**Day of Surgery**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Days 141**	**Day 169**
Visit Window		**+10 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**
Pre-surgery Activities								
Informed Consent	X							
Inclusion Criteria Review	X							
Record ongoing adverse events and concomitant analgesic medication	X							
Train subject in the use of the ePRO system (IWRS) if applicable[c]	X							
Assessment of Pain in Joint to be Replaced (11-point NRS)[d]	X							
Assessment of Functional Status (WOMAC [total hip or knee replacement candidates] or SPADI [total shoulder replacement candidates]) [d]	X							
Provide surgery-related documents (Surgeon's Assessment of Procedural Difficulty and Pathology Specimen Collection/Shipment Guidelines) to Surgeon	X							
Surgery - related Activities								
Obtain Surgeon's Assessment of Procedural Difficulty		X						
Confirm pathology specimens were shipped according to instructions		X						
Ensure required source documents are provided to Endpoint Management Team			X					

Study Activities			Post-Surgery					
Visit Identifier	**Baseline[a]**	**Day 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24/ET**
	Last visit in Study A4091056, A4091057 or A4091058[b] or when notified of TJR surgery	**Day of Surgery**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Days 141**	**Day 169**
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 subjects of contraceptive requirements (if applicable) [e]			X	X	X	X		
Web-based Assessments[f]								
Subject's overall satisfaction with joint replacement surgery (SAPS)			X		X			X
Pain in replaced joint (11-point NRS)			X		X			X
Functional status (WOMAC [total hip and knee replacement subjects] or SPADI [total shoulder replacement subjects] [g]			X		X			X

a. Baseline activities must be conducted at the site.

b. Last visit in Study A4091056, A4091057 or A4091058 can be either the end of study visit or early termination visit; if a TJR occurs or is scheduled to occur after the last subject in the study completes the treatment period in studies A4091059, A4091061 or A4091063 baseline activities would be conducted at either the end of study visit or at the early termination visit in the A4091059, A4091061 or A4091063 study.

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

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

[e] Female subjects of child-bearing potential should be reminded of contraception requirements if less than 112 days (16 weeks) have elapsed since the last dose of subcutaneous investigational product in Study A4091056, A4091057 or A4091058 (or other tanezumab study).

[f] If the subject does not have access to the IWRS via a desktop, laptop or tablet computer for the duration of the study, paper versions of the assessments should be completed by the subject. Completed paper assessments should be returned to the clinical site as soon as possible, but no later than 5 days, after completion of the assessment. Site staff will enter the subject reported outcomes into the IWRS upon receipt of the completed assessment.

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

TABLE OF CONTENTS

LIST OF TABLES

APPENDICES

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 relief of signs and symptoms of osteoarthritis (OA) and management of chronic pain including chronic low back pain (CLBP).

1.2. Background and Rationale

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

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

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

1.2.2. Description of Investigational Product

Tanezumab is a humanized immunoglobulin G Type 2 (IgG_2) monoclonal antibody, derived from a murine precursor by grafting the murine complementarity determining regions onto a human antibody framework, followed by extensive site-directed mutagenesis using proprietary technology to improve binding affinity and specificity. A mutation was performed in the Fc portion of the antibody to decrease its ability to activate complement or to support antibody dependent cell-mediated cytotoxicity.[9,10]

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

1.2.3. Overview of Clinical Studies

A total of 32 clinical studies involving over 11,000 subjects have been conducted with tanezumab as of September 2014. No additional clinical studies have been conducted since that time. Approximately 9810 healthy volunteers or patients have been treated with tanezumab in non cancer pain clinical studies. In patients treated with tanezumab monotherapy or tanezumab + NSAID in completed non cancer pain studies, treatment experience with tanezumab approximates 5900 patient-years of treatment exposure.

A total of 17 clinical studies overall (4 Phase 2 studies and 13 Phase 3 studies) were initiated to provide evidence of efficacy and safety of tanezumab with intravenous (IV) or subcutaneous (SC) administration for the relief of the signs and symptoms of osteoarthritis alone or in combination with NSAIDs. Both IV and SC routes of administration with tanezumab at fixed dose levels of 2.5 mg, 5 mg, and 10 mg every 8 weeks were evaluated in Phase 3 clinical studies of osteoarthritis subjects.

The efficacy and safety of tanezumab IV in chronic low back pain has been evaluated in 3 Phase 2 studies (N=1564). The first was a small Phase 2 proof-of-concept study (A4091004; 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; 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; 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.[11]

In addition to the osteoarthritis studies, 11 Phase 1/2 studies were conducted to examine the efficacy and safety of tanezumab in neuropathic, and visceral pain conditions and 2 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 1 mg to 20 mg or equivalent body-weight adjusted doses up to 100 mg.

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

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

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

In animal studies in rats and non-human primates (described in Section 5.3 of the tanezumab Investigator's Brochure), tanezumab treatment for up to 6 months, with doses producing greater systemic exposure than observed with clinical doses, was associated with lower sympathetic ganglion volume and lower average size of post-ganglionic sympathetic neurons when compared to control animals. All effects were completely reversible following a dosing-free recovery period. In a separate cardiovascular function study in non-human primates (described in Section 5.1 of the tanezumab Investigator's Brochure), functional changes in the cardiovascular system controlled by the sympathetic nervous system were not observed. In March 2015, the FDA lifted the partial clinical hold on tanezumab allowing the resumption of clinical studies for chronic low back pain, osteoarthritis and all other chronic pain conditions.

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

1.2.3.1. Overview of Efficacy in Clinical Studies

In the treatment of pain associated with OA, tanezumab monotherapy doses of 2.5 mg to 10 mg have been shown to provide efficacy that is superior to placebo. In addition, tanezumab monotherapy doses of 5 and 10 mg have demonstrated efficacy above that of NSAIDs. Relative to oxycodone, tanezumab monotherapy doses of 5 mg or 10 mg were shown to have a favorable efficacy profile. Tanezumab 10 mg provided minimal additional benefit over tanezumab 5 mg in the treatment of OA.[11]

In the treatment of CLBP, tanezumab monotherapy doses of 10 mg and 20 mg demonstrated efficacy that was superior to that of placebo and naproxen. Tanezumab 20 mg provided minimal additional benefit over tanezumab 10 mg in the treatment of CLBP.[11]

The available efficacy data in other chronic pain conditions suggests that tanezumab may provide meaningful analgesia in subjects with neuropathic pain, visceral pain and subjects with pain associated with cancer who have metastatic bone pain.[11]

Study A4091056 is a randomized, double-blind, placebo-controlled, multicenter, parallel-group, Phase 3 study of the efficacy and safety of tanezumab when administered by SC injection for 16 weeks compared to placebo in subjects with osteoarthritis of the knee or hip. Approximately 690 subjects will be randomized to one of 3 treatment groups in a 1:1:1 ratio. Subjects will receive a total of two SC injections, separated by 8 weeks:

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

Study A4091056 is designed with a total duration of 40 weeks and will consist of three periods: Screening (37 days), Double-blind Treatment (16 weeks) and Safety Follow-up (24 weeks).

Study A4091057 is a randomized, double-blind, placebo-controlled, multicenter, parallel-group, Phase 3 study of the efficacy and safety of tanezumab when administered by SC injection for 24 weeks compared to placebo in subjects with osteoarthritis of the knee or hip. Approximately 810 subjects will be randomized to one of 3 treatment groups in a 1:1:1 ratio. Subjects will receive a total of three SC injections, separated by 8 weeks:

- tanezumab 2.5 mg;
- tanezumab 5 mg;
- placebo to match tanezumab.

Study A4091057 is designed with a total duration of 48 weeks and will consist of three periods: Screening (37 days), Double-blind Treatment (24 weeks) and Safety Follow-up (24 weeks).

Study A4091058 is a randomized, double blind, active-controlled, multicenter, parallel-group Phase 3 study of the safety, efficacy, and tolerability of tanezumab when administered by SC injection for 56 weeks compared to NSAIDs in subjects with osteoarthritis of the knee or hip. Approximately 3000 subjects will be randomized to one of 3 treatment groups in a 1:1:1 ratio (N=1000/treatment group). Treatment groups will include:

1. SC placebo (to match tanezumab) once every 8 weeks (a total of 7 administrations) plus naproxen 500 mg BID per os (PO), celecoxib 100 mg BID PO, or diclofenac ER 75 mg BID PO through Week 56.
2. Tanezumab 2.5 mg SC once every 8 weeks (a total of 7 administrations) plus placebo matching naproxen, celecoxib or diclofenac ER to maintain blinded BID oral study treatment administration through Week 56.
3. Tanezumab 5 mg SC once every 8 weeks (a total of 7 administrations) plus placebo matching naproxen, celecoxib or diclofenac ER to maintain blinded BID oral study treatment administration through Week 56.

Study A4091058 is designed with a total duration of 80 weeks and will consist of three periods: Screening (37 days), Double-blind Treatment (56 weeks) and Safety Follow-up (24 weeks).

Study A4091059 is a Phase 3 study of the efficacy and safety of tanezumab in subjects with chronic low back pain, Study A4091061 is a Phase 3 study of the efficacy and safety of tanezumab in cancer patients with pain due to bone metastases. Study A4091063 is a Phase 3 study of the safety and efficacy of tanezumab in Japanese adult subjects with chronic low back pain.

1.2.3.2. Overview of Safety in Clinical Studies

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

Table 2. Adverse Drug Reactions in 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 subject 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, 985 subjects with osteoarthritis were treated in 2 studies using SC administration. The adverse event profile of SC administration of tanezumab is comparable to the IV route. The incidence of adverse events, withdrawals due to adverse events, and serious adverse events in subjects treated with tanezumab monotherapy (5-10 mg) was similar to subjects receiving active comparator treatment and increased over placebo-treated subjects. In the tanezumab 2.5 mg monotherapy treatment group, the incidence of adverse events was similar to active comparator while the incidence of withdrawals due to adverse events, and serious adverse events was similar to that of the placebo treatment group. Across the tanezumab monotherapy doses, the rates of adverse events, withdrawals due to adverse events, and serious adverse events were similar with tanezumab 5 mg and 10 mg, and elevated in comparison to tanezumab 2.5 mg. Tanezumab/NSAID combination therapy was associated with higher overall adverse event rates. The relationship of incidence to the dose of tanezumab administered was similar to that observed with tanezumab monotherapy.

Among the most frequently reported adverse events in the controlled Phase 3 osteoarthritis studies, the incidence of peripheral edema, upper respiratory tract infection, fall, arthralgia, back pain, joint swelling, pain in extremity, hypoesthesia, and paresthesia tended to be higher in patients 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 nasopharyngititis and all gastrointestinal-related adverse events. Dose-related increases in the incidence of peripheral edema, joint swelling, osteoarthritis and paresthesia were observed.

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.

1.2.3.2.1. 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.

1.2.3.2.2. Joint Safety

Following the imposition of the clinical hold, a comprehensive investigation and analyses related to joint-safety were conducted, based on tanezumab monotherapy exposure in over 6400 subjects and tanezumab/NSAID combination therapy in 3400 subjects. There were over 5000 subjects who received tanezumab treatment alone or in combination with NSAIDs for 6 months or longer. These data were sufficient to define and characterize the adverse event of concern – rapidly progressive osteoarthritis – and evaluate the risk of rapidly progressive osteoarthritis in the context of the overall benefit-risk profile of tanezumab compared to standard of care. The results and conclusions regarding tanezumab and the other anti-NGF therapies are provided in detail elsewhere.[1,2,3]

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.

1.2.4. Rationale for Study

Measures to better characterize the joint safety issue have been developed and agreed with FDA. This study is 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 study and the duration of the study have been agreed to with the FDA. Every effort will be made to enroll all A4091056, A4091057 and A4091058 subjects who undergo a qualifying total joint replacement into this study however it is acknowledged that to a certain extent the population enrolled in this study will be 'self-selected' and thus there may be subjects with a qualifying total joint replacement who choose not to enter the study.

1.2.5. Rationale for Selected Subject Reported Outcome Measures

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.[12] 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 in this study. 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.[13] 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.[14]

The functional measures chosen for this study 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 will be or 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.[12,15,16]

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.[17,18] 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.

For each of the selected subject reported outcome measures there are data available in the literature. These data will be utilized to contextualize the results of this study.

1.2.5.1. 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 study. Contingency plans will be in place to address system and/or connectivity issues with the IWRS.

However, eligibility for this study 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 Study A4091056, A4091057 or A4091058. Additional considerations which mitigate the concerns about using two methods to collect subject reported outcomes in the same study include that this study has not been formally powered and all analyses will be descriptive rather than inferential.

1.2.6. Summary of Benefit and Risks to Subjects Enrolled in Study A4091064

There is no treatment benefit to subjects participating in Study A4091064 however subjects may derive benefit from the increased post-surgery medical oversight dictated by this study. In addition, information from this study may benefit future patients who receive tanezumab. A detailed discussion of the risks of tanezumab is provided in Section 7 of the Investigator's Brochure. Because no investigational product is administered in Study A4091064, the anticipated investigational product-related risk to subjects participating in Study A4091064 is considered low. However, female subjects who are of childbearing potential and are sexually active and who withdraw from any of the tanezumab studies less than 16 weeks after the last dose of subcutaneous investigational product need to use acceptable methods of contraception due to the potential risk of adverse effects on the fetus if they become pregnant. Finally, although it is considered unlikely given the number of subjects who have been treated with tanezumab to date, it cannot be excluded that some adverse effects of the treatment may become evident after the last administration of the investigational product. The increased post-surgery medical oversight dictated by this study should facilitate recognition of such events if they occur.

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

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objective

- To describe the post-operative outcome of subjects who underwent a total knee, hip, or shoulder replacement while participating in tanezumab Study A4091056, A4091057 or A4091058 (treatment period and safety follow-up period).

2.2. Secondary Objectives

- To compare the post-operative outcome for tanezumab 2.5 mg and 5 mg versus NSAID for subjects who underwent a total knee, hip, or shoulder replacement while participating in tanezumab Study A4091058.

- To describe the post-operative outcome of subjects from the A4091059, A4091061 or A4091063 studies who underwent a total knee, hip, or shoulder replacement.

2.3. Endpoints

Given the design of this study, the following endpoints are considered co-equal:

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

- Subject'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; see also Section 9).

- 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.

3. STUDY DESIGN

This is a Phase 3, multicenter, long-term observational study of subjects from tanezumab Study A4091056, A4091057 or A4091058 (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 study (A4091064), 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 in the study completes the treatment period in studies A4091059, A4091061 or A4091063 may be followed in this study (A4091064).

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

Any subject who expresses a desire to leave this study 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 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 magnetic resonance images (MRI) 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). In addition, blinded summaries of the following data from the parent study (A4091056, A4091057, A4091058 or other studies) will be provided to the Committee members for review for each event undergoing adjudication: demographic and baseline characteristics, medical history and concomitant medications, investigational product 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 (E-DMC), is responsible for ongoing analysis of these outcomes and for informing the sponsor of recommendations made.

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 non-medical 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.

Appropriate members of the investigator's study team are the investigator or sub-investigator.

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. Subject has been randomized and treated with SC investigational product in tanezumab Study A4091056, A4091057, A4091058, A4091059, A4091061 or 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 A4091056, A4091057 or A4091058 **or** after the last subject in the study completes the treatment period in tanezumab Study A4091059, A4091061 or A4091063. 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 study procedures.

4.2. Life Style Guidelines

All female subjects who are of childbearing potential and are sexually active and at risk for pregnancy, and **who withdraw from Study A4091056, A4091057 A4091058, or other tanezumab study less than 16 weeks after the last dose of subcutaneous** investigational product must agree to use two (2) methods of highly effective contraception consistently and correctly **until 112 days (16 weeks) after the last dose of subcutaneous** investigational product. The investigator or his/ or her designee, in consultation with the subject, will confirm the subject has selected the most appropriate forms of contraception for the individual subject from the permitted list of contraception methods (see below), and instruct the subject in their consistent and correct use. Subjects need to affirm that they meet the criteria for correct use of at least two of the selected methods of contraception. The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the schedule of activities and document such conversation in the subject's chart. In addition, the Investigator or his/ or her designee will instruct the subject to call immediately if the selected birth control methods are discontinued or if pregnancy is known or suspected in the subject.

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

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

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

3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the post-vasectomy ejaculate.

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

NOTE: For Sweden and the United Kingdom, please refer to Appendix 4 for Life Style Guidelines for subjects from clinical sites in these countries.

There are no contraception requirements for sexually active female subjects of childbearing potential who withdraw from Study A4091056, A4091057, A4091058 or other tanezumab study more than 16 weeks after the last dose of subcutaneous investigational product.

4.3. 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 supporting study documentation.

5. STUDY TREATMENTS

This is an observational study of subjects who were randomized and treated in tanezumab Study A4091056, A4091057 or A4091058 and who subsequently underwent a total knee, hip or shoulder replacement during the treatment or safety follow-up period. Any subject with a qualifying total joint replacement after the last subject in the study completes the treatment period in studies A4091059, A4091061 or A4091063 may also be followed in this study (A4091064).

There are no protocol defined study medications in this observational study.

Subjects, investigators, study coordinators, clinical site staff, orthopedic surgeons, clinical research associates (CRAs) and staff directly involved with this study at Pfizer and its designees will be blinded to treatment assignment in the parent study (ie, Study A4091056, A4091057, A4091058 or other tanezumab study).

5.1. Concomitant Medication(s)

No medications are specifically prohibited in this observational study.

Subjects who enter into this study <16 weeks after their last dose of subcutaneous investigational product in the parent study (ie, Study A4091056, A4091057, A4091058 or other tanezumab study) 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.

6. STUDY PROCEDURES

Study visit windows are +10 days for activities related to the total joint replacement surgery and ±5 days for activities performed on Weeks 4, 8, 12, 16, 20 and 24. Site staff should make every effort to contact the subject within the protocol defined visit window for Weeks 4, 8, 12, 16, 20 and 24 however, data obtained outside of the visit window while a protocol 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 assigned study monitor or study clinician 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.

6.1. Baseline Visit

Baseline information for this study 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 A4091056, A4091057 or A4091058 (End of Study or Early Termination Visit) or occur when the site is notified of a planned total joint replacement surgery. If a total joint replacement occurs or is scheduled to occur after the last subject in the study completes the treatment period in Study A4091059, A4091061 or A4091063 baseline activities could be conducted at either the end of study visit or at the early termination visit in Study A4091059, A4091061 or A4091063. 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 ePRO system (IWRS) and in their responsibilities for data entry in compliance with the 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 Study A4091064 should complete the aforementioned assessments on paper for the duration of Study A4091064. 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 Study A4091064.

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.

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 for the duration of the study should be provided with paper copies of the subject reported outcomes assessments for subsequent entry into the IWRS by site staff.
- Subjects should be instructed on the timing of assessments and the need to return the assessments to the site as soon as possible, but no later than 5 days, after completion of the assessment.
- Study site staff must contact the subject's orthopedic surgeon to discuss the completion of the required forms and specimen collection and handling. The surgeon will be provided with the surgery related documents (Surgeon's Assessment of Procedural Difficulty and instructions for the shipment of pathology specimens).
- If less than 112 days (16 weeks) have elapsed since the last dose of subcutaneous investigational product in Study A4091056, A4091057 ,A4091058 or other tanezumab study, female subjects of child-bearing potential should be reminded of contraceptive requirements.

6.2. Day of Surgery Day 1 (+10 days)

During this interval, sites should ensure receipt of a completed Surgeon's Assessment of Procedural Difficulty and confirm that pathology specimens were shipped according to instructions. Required source document collection (eg, operative report and discharge summary) should begin in this interval.

Sites will be requested to submit required source documentation to the Endpoint Management Team as soon as possible, and ideally within 29 ±5 days, after the total joint replacement surgery (ie, by the time the Week 4 visit occurs provided the source documentation has been completed).

6.3. Week 4 Day 29 (±5 days)

Site staff should contact the subject via telephone to:

- Query for adverse events.
- Query for concomitant analgesic medication use (record dose, dosing regimen and reason for use).
- Query about physical rehabilitation activities subsequent to the total joint replacement surgery.

During the telephone call, site staff should instruct the subject to complete the following assessments either via the IWRS or via paper, as established at the Baseline Visit:

- Pain in Replaced Joint (11-point NRS).
- Functional status (WOMAC for subjects with a total knee or hip replacement or SPADI for subjects with a total shoulder replacement); NOTE: the WOMAC and SPADI should be completed in their entirety.
- Overall satisfaction with joint replacement surgery (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. Site staff will enter the subject reported outcomes into the IWRS upon receipt of the completed assessment.
- If less than 112 days (16 weeks) have elapsed since the last dose of subcutaneous investigational product in Study A4091056, A4091057, A4091058 or other tanezumab study, remind female subjects of child-bearing potential of contraceptive requirements.
- Confirm the approximate timing of the next telephone call.

6.4. Week 8 Day 57 (±5 days)

Site staff should contact the subject via telephone to:

- Query for adverse events.
- Query for concomitant analgesic medication use (record dose, dosing regimen and reason for use).

At the conclusion of the telephone call, site staff should:

- If less than 112 days (16 weeks) have elapsed since the last dose of subcutaneous investigational product in Study A4091056, A4091057,A4091058 or other tanezumab study, remind female subjects of child-bearing potential of contraceptive requirements.
- Confirm the approximate timing of the next telephone call.

6.5. Week 12 Day 85 (±5 days)

Site staff should contact the subject via telephone to:

- Query for adverse events.
- Query for concomitant analgesic medication use (record dose, dosing regimen and reason for use).
- Query about physical rehabilitation activities subsequent to the total joint replacement surgery.
- Query for additional or corrective procedures related to the total joint replacement surgery.

During the telephone call, site staff should instruct the subject to complete the following assessments either via the IWRS or via paper, as established at the Baseline Visit:

- Pain in Replaced Joint (11-point NRS).
- Functional status (WOMAC for subjects with a total knee or hip replacement or SPADI for subjects with a total shoulder replacement); NOTE: the WOMAC and SPADI should be completed in their entirety.
- Overall satisfaction with joint replacement surgery (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. Site staff will enter the subject reported outcomes into the IWRS upon receipt of the completed assessment.

- If less than 112 days (16 weeks) have elapsed since the last dose of subcutaneous investigational product in Study A4091056, A4091057, A4091058 or other tanezumab study, remind female subjects of child-bearing potential of contraceptive requirements.

- Confirm the approximate timing of the next telephone call.

6.6. Week 16 Day 113 (±5 days)

Site staff should contact the subject via telephone to:

- Query for adverse events.

- Query for concomitant analgesic medication use (record dose, dosing regimen and reason for use).

At the conclusion of the telephone call, site staff should:

- If less than 112 days (16 weeks) have elapsed since the last dose of subcutaneous investigational product in Study A4091056, A4091057, A4091058 or other tanezumab study, remind female subjects of child-bearing potential of contraceptive requirements.

- Confirm the approximate timing of the next telephone call.

6.7. Week 20 Day 141 (±5 days)

Site staff should contact the subject via telephone to:

- Query for adverse events.

- Query for concomitant analgesic medication use (record dose, dosing regimen and reason for use).

At the conclusion of the telephone call, site staff should:

- Confirm the approximate timing of the next telephone call.

6.8. Week 24 Day 169 (±5 days)

Site staff should contact the subject via telephone to:

- Query for adverse events.

- Query for concomitant analgesic medication use (record dose, dosing regimen and reason for use).

- Query about physical rehabilitation activities subsequent to the total joint replacement surgery.
- Query for additional or corrective procedures related to the total joint replacement surgery.

During the telephone call, site staff should instruct the subject to complete the following assessments either via the IWRS or via paper, as established at the Baseline Visit:

- Pain in Replaced Joint (11-point NRS).
- Functional status (WOMAC for subjects with a total knee or hip replacement or SPADI for subjects with a total shoulder replacement); NOTE: the WOMAC and SPADI should be completed in their entirety.
- Overall satisfaction with joint replacement surgery (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. Site staff will enter the subject reported outcomes into the IWRS upon receipt of the completed assessment.

6.9. Subject Withdrawal/Early Termination

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

If a subject cannot be contacted within the window for a scheduled visit, every effort should be made to contact the subject outside of the visit window. 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. 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, request that the subject return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events (AEs).

If the subject is willing, the investigator should 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 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 (SAPS).

Subjects not utilizing the IWRS should be reminded to return paper based assessments to the site as soon as possible, but no later than 5 days, after completion of the assessment.

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.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol 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 protocol required procedure 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. Surgeon's Assessment of Procedural Difficulty

Following the total joint replacement surgery, the orthopedic surgeon performing the surgery will be asked to answer the following question:

"Taking into consideration the subject's medical history and physical condition prior to surgery would you classify the operative procedure as:

1. Uneventful; or
2. Minor complications; or
3. Major complications.

If the category of minor or major complications is chosen, the surgeon will be requested to specify the complication(s).

7.2. Pathology Specimens

Surgeons will be requested to ship pathology specimens from the total joint replacement surgery to a central laboratory for processing and/or 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.

7.3. Telephone-based Assessments

Post-surgery, subjects will be contacted monthly via telephone by study site personnel.

7.3.1. 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 syndroma) 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 and adverse event (if applicable) forms. Adverse events will be reported where applicable as described in Section 8.

Subjects reporting adverse events (any seriousness or severity) with preferred terms of bradycardia, syncope, orthostatic hypotension, anhidrosis or hypohidrosis should be further evaluated for the presence of sympathetic autonomic neuropathy 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.

7.3.2. 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).

7.3.3. Physical Rehabilitation Activities

At the Week 4, 12 and 24 post-surgery telephone contacts, subjects will be queried for 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).

7.3.4. 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).

7.4. Web-based Assessments

7.4.1. Overall Satisfaction with 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.

7.4.2. 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 replaced joint) the past 24 hours.

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

At Baseline and at Weeks 4, 12 and 24 following total joint replacement surgery, subjects will be asked to indicate their average pain in the joint to be replaced (pre-surgery) or the replaced joint (post-surgery) via the IWRS or by paper if the subject does not have access to the internet via a desktop, laptop or tablet computer. When completed on paper, the subject will be requested to return the assessment to the site as soon as possible, but no later than 5 days, after completion of the assessment.

7.4.3. 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 will be or 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.

7.4.3.1. 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.

7.4.3.1.1. 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. This may or may not have been the index joint in Study A4091056, A4091057 or A4091058.** 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.

7.4.3.1.2. 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. This may or may not have been the index joint in Study A4091056, A4091057 or A4091058.** 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.

7.4.3.1.3. 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. This may or may not have been the index joint in Study A4091056, A4091057 or A4091058.** 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 1.

7.4.3.2. 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 at 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 2.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events (AEs)

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

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

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

8.2. Reporting Period

Subjects entering study A4091064 may have left Study A4091056, A4091057 or A4091058 at variable intervals relative to the last dose of subcutaneous investigational product in Study A4091056, A4091057 or A4091058.

There is no investigational product administered in study A4091064.

The reporting requirements for Study A4091056, A4091057 and A4091058 are as follows:

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

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

- AEs (serious and non-serious) should be recorded on the CRF from the time the subject has taken at least one dose of study treatment through last subject visit.

SAEs should be reported to the respective parent study A4091056 / A4091057 / A4091058 using the Clinical Trial SAE Report Form (see Section 8.12.1 of the parent study protocol).

An AE/SAE should be recorded on the A4091064 CRF from the time the subject has signed the informed consent document through last subject visit in study A4091064.

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;
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.4. Medication Errors

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

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

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

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

8.5. Abnormal Test Findings

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

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

- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or

- Test result is considered to be an AE by the investigator or sponsor.

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

8.6. Serious Adverse Events

An serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;

- Is life-threatening (immediate risk of death);

- Requires in subject hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

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

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

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

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to run LFTs because of clinical sign/symptom presentation in a subject, such LFT results should be handled and followed up as described below.

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) concurrent with abnormal elevations in total bilirubin 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 ≥3 times the upper limit of normal (x ULN) concurrent with a total bilirubin ≥2 x ULN with no evidence of hemolysis and an alkaline phosphatase ≤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 ≥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** ≥3 normal 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 AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/ international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

8.7. Hospitalization

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

Hospitalization does not include the following:

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

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

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

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

8.8. Severity Assessment

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

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

8.9. Causality Assessment

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

In addition, if the investigator determines 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 (EDP)

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

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

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

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

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

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

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

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

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

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

8.10.1. Additional Post-Natal Follow-up

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

8.11. Occupational Exposure

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

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 CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

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

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

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

8.13. Eliciting Adverse Event Information

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

8.14. Reporting Requirements

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

8.14.1. Serious Adverse Event Reporting Requirements

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

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

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

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

8.14.2. 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. 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 the summary and descriptive 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 planned analyses will also be reflected in a protocol amendment.

9.1. Sample Size Determination

This study 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 A4091056, A4091057 or A4091058 (treatment or safety follow-up period). In addition subjects with a qualifying total joint replacement after the last subject in the study completes the treatment period in Study A4091059, A4091061 or A4091063 may be included. The number of subjects who will enroll in this study is unknown but is estimated to be less than 250 subjects. Also unknown is the distribution of subjects across treatment groups (ie, the treatment given in Study A4091056, A4090157, A4091058, or other tanezumab study). Therefore, it is predicted that there will be insufficient statistical power to perform statistical inferential analyses. All analyses will be descriptive in nature.

9.2. Analysis of Endpoints

All subjects enrolled in the study who have a total joint replacement will be included in the summary tables.

A summary of data will be shown using subjects from study A4091058. The incidence of subjects with a total joint replacement will be summarized for all subjects, and split by Study A4091058 treatment group. These summaries will be shown as percentages, and for exposure-adjusted rates (using Study A4091058 treatment and follow-up period up to the time of surgery). Comparisons of the total joint replacement rates will be made between tanezumab versus active comparator treatment groups, using risk differences and ratios with 95% confidence intervals. Summaries of the time to total joint replacement surgery and time to first symptom (leading to total joint replacement surgery) will be summarized using Kaplan-Meier survival estimates from the date of first subcutaneous dose in Study A4091058, and shown overall, and split by Study A4091058 treatment group where there are sufficient numbers of subjects. A further summary of the incidence of subjects with total joint replacements will be shown separately for studies A4091056, A4091057, A4091059, A4091061 and A4091063, if applicable. Similar summaries by study will be shown for adjudication outcomes. The summary of time to total joint replacement surgery and time to first symptom (leading to total joint replacement surgery) will also be performed using data for subjects from Studies A4091056 and A4091057.

Unless otherwise stated, data from this study will be presented at Baseline and Weeks 4, 12, and 24 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 when Baseline data are available and where relevant. Data will be shown overall, and split by treatment group. Data on surgical difficulty and outcomes, and subject safety data will be summarized by study, with an additional combined summary for the subjects from the osteoarthritis studies.

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 stratified by surgery type (hip, knee or shoulder) and 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 stratified by surgery type (hip, knee or shoulder) and summarized. Reponses to the question "How satisfied are you with the results of your surgery?" will also be stratified by surgery type (hip, knee or shoulder) and 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. For these assessments, change from Baseline summary data are not relevant and will not 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 Baseline summaries).

Adverse events and concomitant analgesic medications will be collected for each subject during the study according to the Schedule of Assessments. Standard safety reporting tables will summarize and list these safety data.

In addition, 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[19,20] will be used for guidance in developing the list of post-surgical complications. The list of post-surgical complications will be developed during Study A4091064 and finalized prior to Study A4091058 database lock.

Separate adverse event summaries by parent study treatment group for adverse events of decreased sympathetic function will be presented.

For subjects from study A4091058 and for subjects from any of the osteoarthtitis studies, summaries of total joint replacement, adjudication event rates and post-surgical outcomes will be shown for subgroups including age, gender, body-mass index (BMI), baseline Kellgren-Lawrence grade of the replaced joint (knees and hips only) and number of joints with OA.

9.3. Data Monitoring Committee (DMC)

This study will use an external data monitoring committee (EDMC).

An independent, E-DMC has been re-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) general adverse events and serious adverse events on a regular basis throughout the tanezumab clinical program. The E-DMC will have written operating procedures and a Charter, including a specific description of the scope of their responsibilities.

Adverse events of syncope, bradycardia, orthostatic hypotension, anhidrosis or hypohidrosis will be designated as adverse events of interest. These adverse events 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 be responsible for ongoing monitoring of the safety of subjects in the program according to the charter. If the blinded Adjudication Committee (see Section 9.4) 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 protocol-based stopping criteria, an urgent, ad hoc assessment of the events will be made by the E-DMC.

Any recommendations made by the E-DMC to alter the conduct of one or more of the studies 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.

9.4. External Adjudication Committee

A blinded Adjudication Committee consisting of external experts in orthopedic surgery, rheumatology, orthopedic pathology, or radiology with expertise in subjects with end stage osteoarthritis and osteonecrosis will be convened. The Adjudication Committee will have written operating procedures and a Charter, including a specific description of the scope of their responsibilities. In general, the Adjudication Committee will be asked to review all possible or probable joint-related safety events identified by the Central Reader, total joint replacements as well as investigator-reported adverse events of osteonecrosis, rapidly progressive osteoarthritis, or 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.

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

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 investigative 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 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 /Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer. The investigator should also receive the approval from the national competent authority before implementing a substantial amendment.

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

12.2. Ethical Conduct of the Study

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

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

12.3. Subject Information and Consent

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

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

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

The informed consent document(s) used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/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

Subject recruitment efforts are not required for this study because this is an observational extension study.

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

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

13.2. End of Trial in All Other Participating Countries

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

14. SPONSOR DISCONTINUATION CRITERIA

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

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

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 trial 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 multicenteer 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 Clinical Study Agreement.

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. 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.

2. Hertz S, Fields E. Addendum to the Background Package for the March 12, 2012, AAC Meeting, Regarding the Agency Adjudication of Cases of Joint Replacements Occurring in Clinical Trials of Anti-NGF Agents. In; March 2, 2012. URL:http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/ucm295201.htm. Access date: April 4, 2012.

3. Rappaport BA. FOOD AND DRUG ADMINISTRATION Center for DrugEvaluation andResearch:BackgroundMaterials.February13,2012.URL:http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/ucm295201.htm. Access date: April 4, 2012.

4. Bennett DLH, McMahon SB, Rattray M, Shelton D. Nerve growth factor and sensory nerve function. In "Pain and Neurogenic Inflammation", eds. SD Brain and PK Moore. Birkhauser, Basel. 1999.

5. Woolf CJ, Safieh-Garabedian B, Ma QP, Crilly P, Winter J. Nerve growth factor contributes to the generation of inflammatory sensory hypersensitivity. Neuroscience 1994; 62:327-31.

6. McMahon SB, Bennett DLH, Priestley JV, Shelton DL. The biological effects of endogenous nerve growth factor on adult sensory neurons revealed by a trkA IgG fusion molecule. Nature Med 1995; 1:774-780.

7. Safieh-Garabedian B, Poole S, Allchome A, Winter J, Woolf CJ. Contribution of interleukin 1 beta to the inflammation induced increase in nerve growth factor levels and inflammatory hyperalgesia. Br J Pharmacol 1995; 115:1265-1275.

8. Woolf CJ, Allchorne B, Safieh-Garabedian B, Poole S. Cytokines, nerve growth factor and inflammatory hyperalgesia: the contribution of tumor necrosis factor α. Br J Pharmacol 1997; 121:417-424.

9. Armour KL, Clark MR, Hadley AG, Williamson LM. Recombinant human IgG molecules lacking Fcgamma receptor I binding and monocyte triggering activities. Eur J Immunol 1999; 29(8):2613-2624.

10. Armour KL, van de Winkel JG, Williamson LM, Clark MR. Differential binding to human FcgammaRIIa and FcgammaRIIb receptors by human IgG wild type and mutant antibodies. Mol Immunol 2003; 40(9):585-593.

11. February 2015 Tanezumab (PF-04383119) Investigator Brochure.

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

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

14. Hawker GA, et al. Measures of adult pain. Arthritis Care Res 2011;63:S240-S252.

15. 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.

16. Rogers JC and Irrgang JJ. Measures of adult lower extremity function. Arthritis Care Res 2003;49:S67-S84.

17. Angst F, et al. Measures of adult shoulder function. Arthritis Care Res 2011;63:S174-S188.

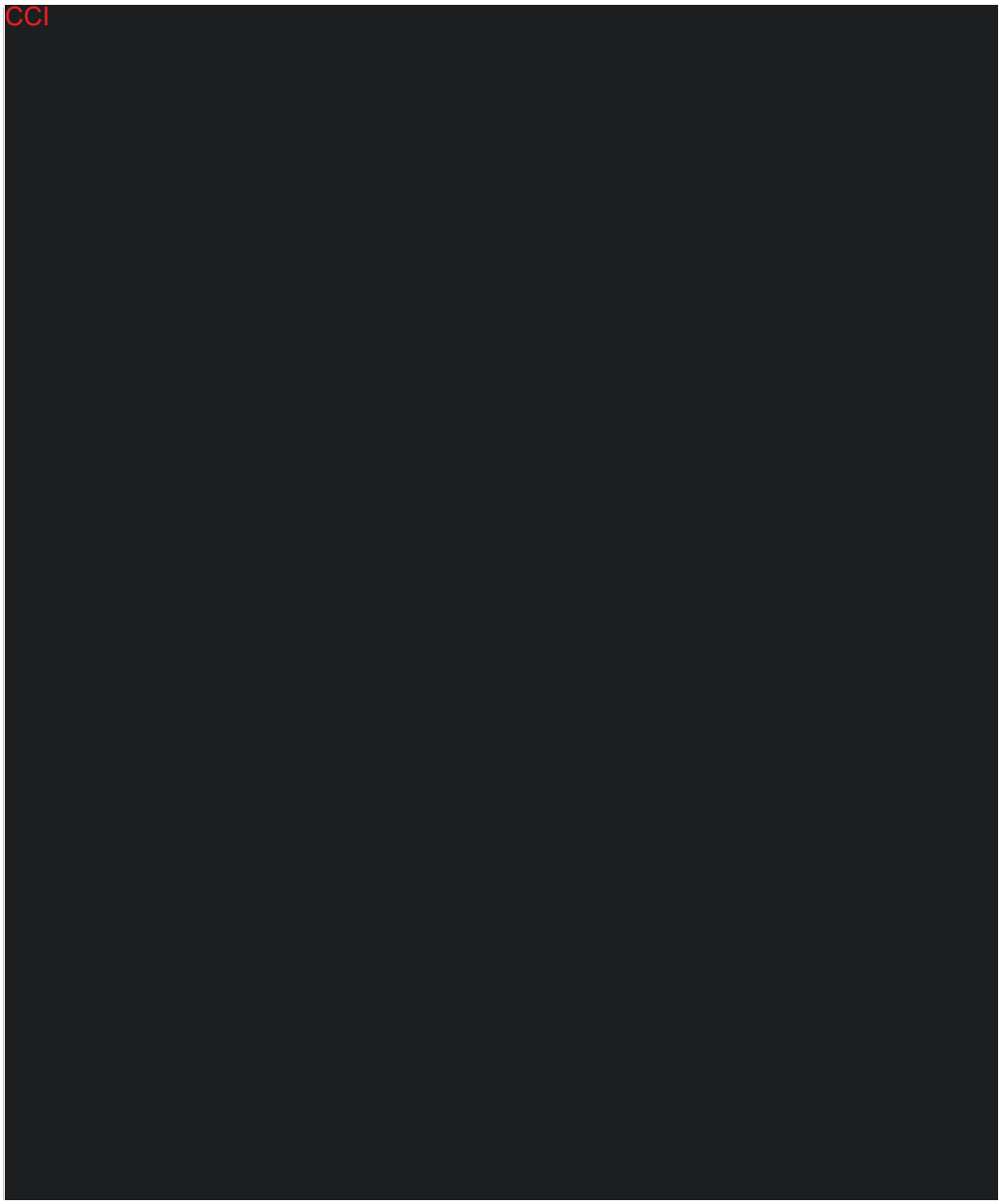
18. Roy J-S, MacDermid JC and Woodhouse LJ. Measuring shoulder function: a systemic review of four questionnaires. Arthritis Care Res 2009; 61:623-632.

19. 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.

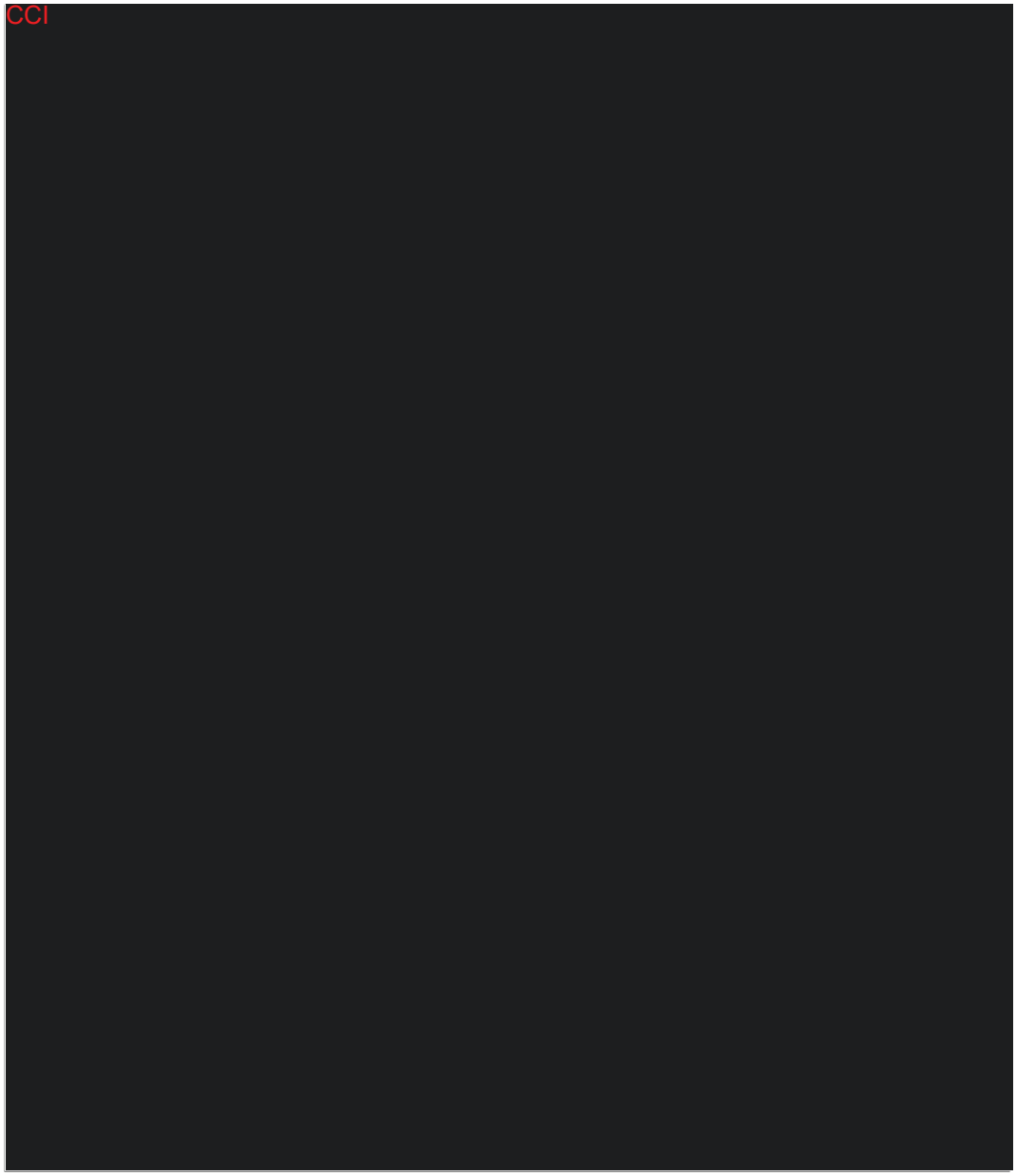
20. Bohsali KI, Wirth MA and Rockwood CA. Complications of total shoulder arthroplasty. J Bone Joint Surgery 88:2006; 2279 – 2292.

Appendix 1. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

WOMAC Osteoarthritis Index NRS3.1

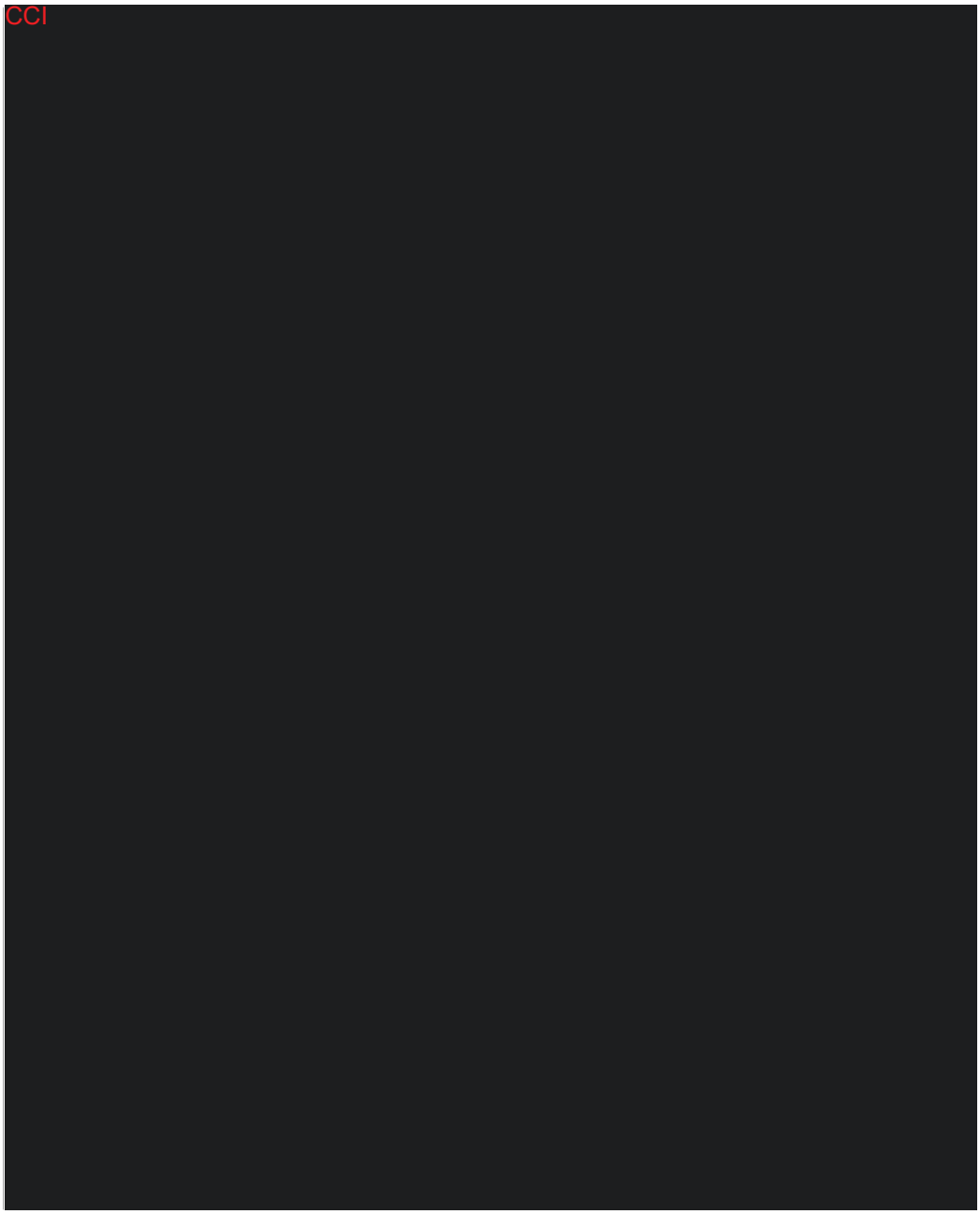


WOMAC Osteoarthritis Index NRS3.1

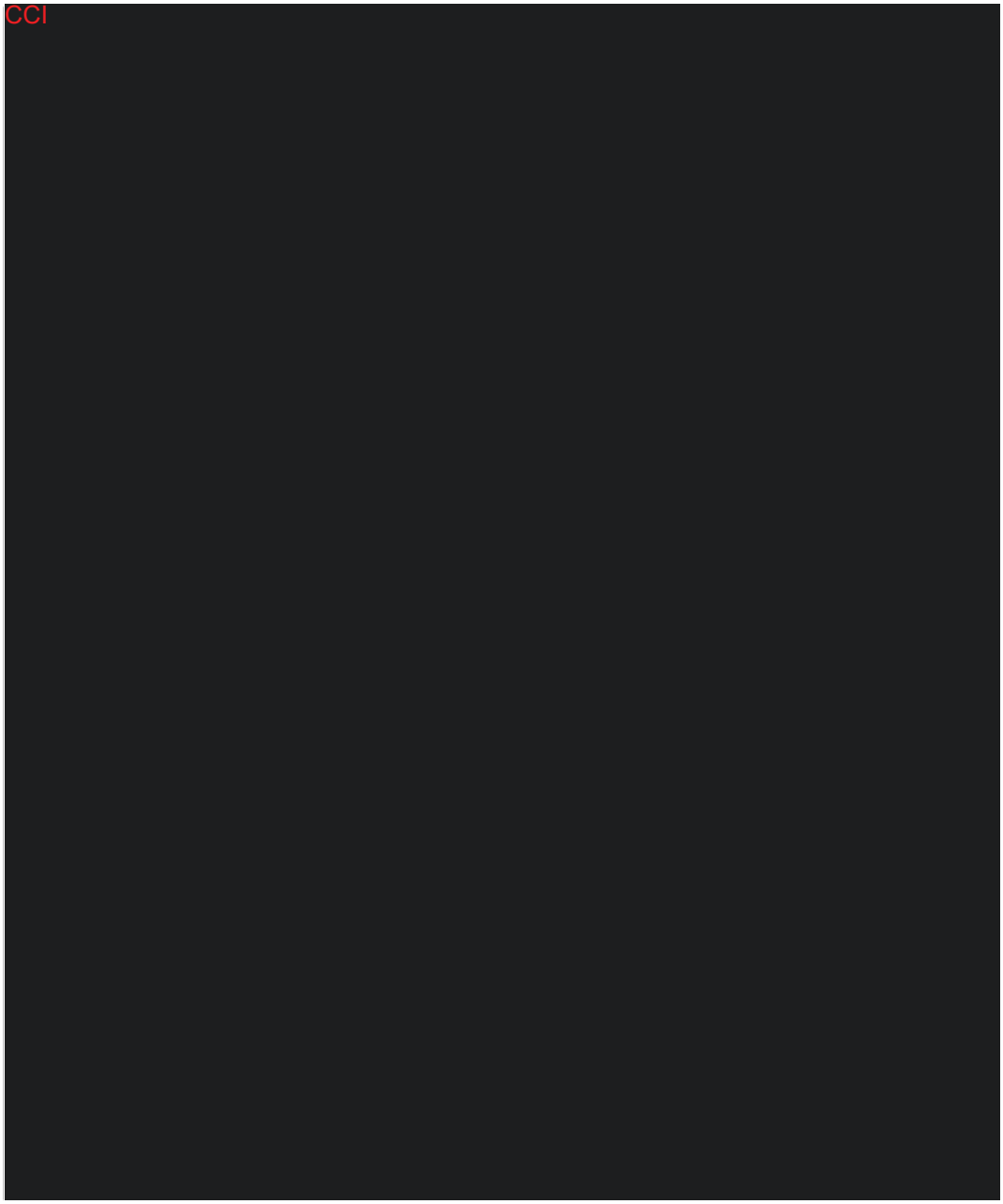


WOMAC Osteoarthritis Index NRS3.1

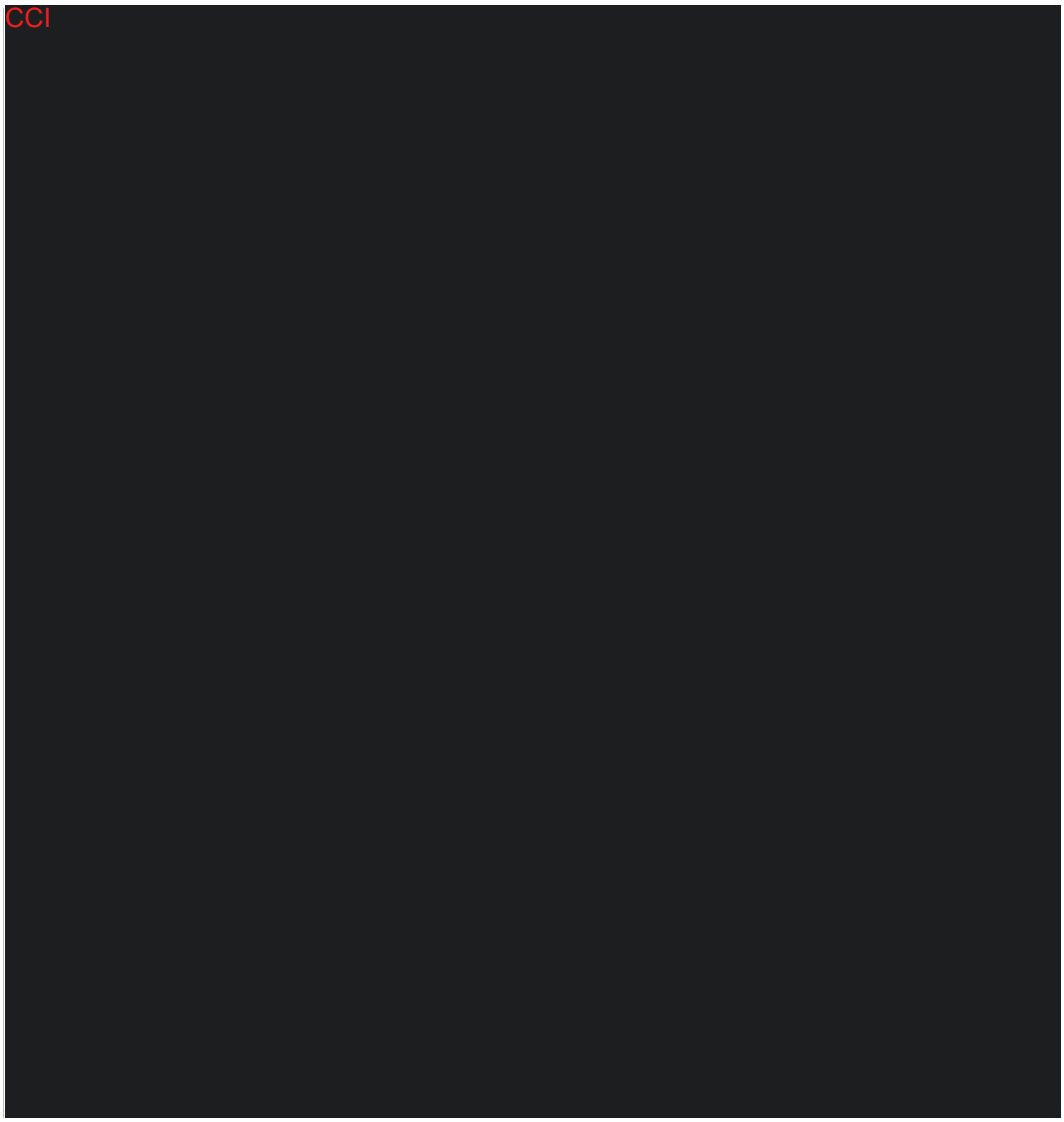
WOMAC Osteoarthritis Index NRS3.1



WOMAC Osteoarthritis Index NRS3.1



WOMAC Osteoarthritis Index NRS3.1



Appendix 2. 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

Source: Roach KE, Budiman-Mak E, Songsiridej N, Lertratanakul Y. Development of a shoulder pain and disability index. *Arthritis Care Res*. 1991 Dec;4(4):143-9.

Appendix 3. Abbreviations

This is a list of abbreviations used in the protocol.	
Abbreviation	**Term**
AE	adverse event
AEMPS	Agency on Medicinal Products and Medical Devices (Spain)
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice a day
CLBP	chronic low back pain
CRF	case report form
CRA	Clinical Research Associate
CSA	clinical study agreement
CTA	clinical trial application
DAAAP	Division of Analgesia, Anesthetic, and Addiction Products
DEXA	dual energy x-ray absorptiometry
EC	ethics committee
EDP	exposure during pregnancy
E-DMC	External Dafety Monitoring Committee
ePRO	electronic patient reported outcome
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IND	investigational new drug application
Ig	immunoglobulin
IgG2	immunoglobulin G Type 2
IRB	institutional review board
IL	interleukin
INR	International Normalize Ratio
IUD	intrauterine device
IV	intravenous
IWRS	interactive web response system
LFT	liver function test
LOCF	Last Observation Carried Forward
MHRA	Medicines and Healthcare products Regulatory Agency (United Kingdom)
MRI	magnetic resonance imaging
NGF	nerve growth factor
NGFI	nerve growth factor inhibitor
NRS	numeric rating scale
NSAID	non-steroidal anti-inflammatory drug
NSC	Neuropathy Symptom and Change
OA	osteoarthritis

PEI	Paul Ehrlich Institute (Germany)
PCD	primary completion date
PT	prothrombin time
RPOA	rapidly-progressive osteoarthritis
SAE	serious adverse event
SAPS	Self-Administered Patient Satisfaction Scale
SC	subcutaneous
SPADI	Shoulder Pain and Disability Index
SPONK	spontaneous osteonecrosis of the knee
SRSD	single reference safety document
TNFα	tumor necrosis factor alpha
trkA	tropomyosin receptor kinase A
ULN	upper limit of normal
US	United States
WOMAC	Western Ontario and McMaster University Osteoarthritis Index

Appendix 4. Lifestyle Guidelines for Subjects from Sites in Sweden and the United Kingdom

All female subjects who are of childbearing potential and are sexually active and at risk for pregnancy, and **who withdraw from Study A4091056, A4091057 A4091058, or other tanezumab study less than 16 weeks after the last dose of subcutaneous** investigational product must agree to use one (1) method of highly effective contraception consistently and correctly **until 112 days (16 weeks) after the last dose of subcutaneous** investigational product. The investigator or his/ or her designee, in consultation with the subject, will confirm the subject has selected the most appropriate form of contraception for the individual subject from the permitted list of contraception methods (see below), and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for correct use of the selected method of contraception. The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the schedule of activities and document such conversation in the subject's chart. In addition, the Investigator or his/ or her designee will instruct the subject to call immediately if the selected birth control methods are discontinued or if pregnancy is known or suspected in the subject.

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

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

        - Oral

        - Intravaginal

        - Transdermal

    - Progestogen-only hormonal contraception associated with inhibition of ovulation[1]:

        - Oral

        - Injectable

        - Implantable

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

3. Bilateral tubal occlusion.

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

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

There are no contraception requirements for sexually active female subjects of childbearing potential who withdraw from Study A4091056, A4091057, A4091058 or other tanezumab study more than 16 weeks after the last dose of subcutaneous investigational product.

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

Source: Clinical Trial Facilitation Group. Recommendations related to contraception and pregnancy testing in clinical trials [Internet]. Germany: Heads of Medicines Agencies (HMA); 2014 [2014 Sep 15; cited 2015 Aug 12]. Available from: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf.