PROTOCOL A4091064

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

STATISTICAL ANALYSIS PLAN (SAP)

Version: 4.0 (Final)

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Date: 2nd July 2019

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APPENDICES

1. AMENDMENTS FROM PREVIOUS VERSION(S)

This is the third amendment to the previously approved SAP (version 3.0 on 29Mar2019). Summary of changes of this amendment versus the previously amended SAP (version 2.0) include:

- Updated the analysis of additional or corrective procedure, post-surgical complications, AE special interest, adjudicated outcome, under Section 6 and 8.2.1,
- Updated subgroup analysis (removed by age, gender, BMI, KL grade, number of joint of OA and added sub-population for subjects who had RPOA, Primary ON, SIF or NPOA for three endpoints) under Section 6.3, and Section 8.2.1. The first group of subgroup analyses are recognized as less informative due to small N based on the discussion with clinical. Subgroups were added for considering joint safety outcomes of parent studies regardless of the number of subjects.
- Updated summary of analysis based on the discussion with team under Section 8.2.2.

This is the second amendment to the previously approved SAP (version 2.0 on 19June2018). Summary of changes of this amendment versus the previously amended SAP (version 2.0) include:

- Clarified the status of patients from A4091059, A4091061 and A4091063 under Section 2.2,
- Changed the name of clinical research organization name from “inVentiv" to “Syneos” due to integration of the companies under Section 3,
- Changed the definition of analysis set from Full Analysis Set to Safety Analysis Set with considering endpoint characteristics under Section 5, and Section 8,
- Updated preferred term of adverse events about the abnormal peripheral sensation, and the sympathetic nervous system under Section 6.1,
- Updated analysis methodology under Section 8,
- Updated total joint replacement and adjudicated outcome under Section 8.1.3,
- Added subpopulation summary table about RPOA (type 1 and type 2), RPOA (type 1), RPOA (type 2), Primary ON, SIF and NPOA under Section 8.2.1, and removed all other subgroup analysis under Section 8.2.1 and 8.2.2,
- Updated summary of analysis (Section 8.2.2) based on above section

This is the first amendment to the previously approved SAP (version 1.0 on 01October2015). Summary of changes of this amendment versus the previously amended SAP (version 1.0) include:

- Amended the possibility of adverse events summarize of decreased sympathetic function under Section 8.2.1.
- Added to summarize for combined all osteoarthritis studies for our clarity under Section 8.
- Added the unblinding plan related to section 5 of A4091064 protocol under Appendix 2 of this document.

2. INTRODUCTION

Note: in this document any text taken directly from the protocol is ***italicised***.

2.1. 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). However, due to change of the enrolment strategy, patients will not be enrolled from A4091061 and A4091063. In addition, patients were not enrolled from A4091059. The patients with TJR in these three studies will be summarized within each individual study or be listed if there are too few to summarize.

This study is designed with a total duration of subject follow-up of 24 weeks after the total joint replacement surgery.

*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 (*Interactive Web-Response System, *IWRS), average pain in the replaced joint (IWRS), the subject's level of function and activity in the replaced joint (IWRS) and physical rehabilitation activities (telephone interview) will be made at Weeks 4, 12 and 24. At Weeks 12 and 24, subjects will be queried during the telephone interview as to whether any additional or corrective procedures related to the total joint replacement are planned.*

All events of total knee, hip or shoulder replacement will be reviewed by the Joint Safety Adjudication Committee (Adjudication Committee) established for the tanezumab clinical program. This Committee will adjudicate in an independent and blinded fashion if the event is primary osteonecrosis, worsening OA (further sub-divided into rapidly progressive OA [RPOA] type 1 or type 2, normal progression of OA or not enough information to distinguish between RPOA and normal progression of OA), subchondral insufficiency fracture, pathologic fracture, other (with diagnosis specified) or not enough information to specify a diagnosis.

2.2. Study Objectives

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 the A4091059, A4091061 or A4091063 studies who underwent a total knee, hip, or shoulder replacement*

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

The final analysis for this study will be performed after the database has been released.

The incidence of subjects with total joint replacements, and resulting adjudicated outcomes will be summarized throughout the tanezumab program. This includes the parent studies of this protocol (A4091056, A4091057, and A4091058), this study itself, and other tanezumab studies (A4091059, A4091061, and A4091063). These analyses will be produced for the Data Monitoring Committee (DMC) and will be unblinded to the DMC members. These analyses will be produced by a separate unblinded group at Syneos who are separate from the corresponding study team at both Syneos and Pfizer.

Information from this study will be blinded for the parent study treatment group until the parent study itself has been unblinded.

In all cases the adjudication of joint safety events is made in a blinded fashion by the adjudication committee.

Interim analyses of these data may be produced for inclusion in a regulatory submission. In this case, a snap-shot of the database will be taken and stored. If this interim analysis occurs, then all parent study databases would have been finalized and those studies unblinded, therefore it is not envisioned that subjects would be unblinded due to this interim analysis.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

There is no given sample size for this study, both for the overall number of subjects and for the number of subjects in any single (parent study) treatment group. Data will be summarized overall and then by parent study and parent study treatment group. Given the likely lack of statistical power for treatment comparisons, no inferential testing will be performed, and all summaries and analyses will be descriptive in nature.

4.2. Statistical Decision Rules

There will be no statistical inferential testing in this study.

5. ANALYSIS SETS

5.1. Full Analysis Set

Not Applicable.

5.2. 'Per Protocol' Analysis Set

There will be no per-protocol analysis set defined for this study.

5.3. Safety Analysis Set

The 'Safety Analysis Set' (SAS) is the analysis set for all analyses. It consists of all treated subjects who enrolled in Study A4091064, and who have a qualifying total joint replacement for Study A4091064. This analysis set is used in the presentations of all data summaries and listings and is labeled as the 'Safety Analysis Set' or 'SAS'.

5.4. Other Analysis Sets

No other analysis sets are defined.

5.5. Treatment Misallocations

Parent study treatment allocation will be based on the actual treatment group received. Where a subject received an incorrect treatment (versus the planned treatment group as required by the randomisation procedure) then the subject will be allocated to a treatment group received where this matches a treatment group from that study or other studies, ie, from the following list:

- Placebo SC;
- Tanezumab 2.5mg;
- Tanezumab 2.5/5mg (tanezumab 2.5mg at Baseline and tanezumab 5mg at Week 8);
- Tanezumab 5mg;
- Tanezumab 10mg;
- NSAID (with placebo SC);
- Tramadol (with placebo SC).

Where the subject's actual treatment does not match one of the groups listed above, then the subject will be allocated to a treatment group based on the highest dose of tanezumab received (eg, if a subject received placebo SC at Baseline and tanezumab 5mg at Week 8 the subject would be allocated to the tanezumab 5mg group).

5.6. Protocol Deviations

Given this is an observational safety study and there is no per-protocol analysis set being used, then no deviations for the purpose of analyses will be defined.

5.6.1. Deviations Assessed Prior to Randomization

Not applicable.

5.6.2. Deviations Assessed Post-Randomization

Not applicable.

6. ENDPOINTS AND COVARIATES

6.1. 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).*
- *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* Shoulder Pain and Disability Index *(SPADI) in the replaced shoulder (subjects undergoing total shoulder replacement surgery only).*

- *Concomitant analgesic medication use.*

The WOMAC subscale scores of Pain, Stiffness and Physical Function are calculated as the mean of the 5, 2 and 17 items, respectively, from the WOMAC questionnaire. Each item is scored on a 0-10 numerical rating scale (NRS), and so the WOMAC subscale scores themselves have a range of 0-10, with 0 being the best response.

The Average Pain in the replaced joint will be scored on a 0-10 NRS scale, where 0 is 'no pain' and 10 is the 'worst possible pain'.

The Self-Administered Patient Satisfaction (SAPS) contains the following four 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.

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). The pain dimension is calculated as the sum of non-missing scores divided by the maximum possible score (50 with no missing items) multiplied by 100. The disability (function) dimension score is calculated as the sum of non-missing scores divided by the maximum possible score (80 with no missing items) multiplied by 100. The dimension scores can be calculated with up to 2 missing items, however if there are >2 missing items from a dimension then that dimension cannot be scored, and is set to missing. A SPADI total score will be calculated as the mean of the pain and disability (function) dimensions.

The Surgeon's Assessment of Procedural Difficulty asks the question "*Taking into consideration the subject's medical history and physical condition prior to surgery would you classify the operative procedure as*" with the following three possible outcome categories:

- Uneventful;
- Minor complications;
- Major complications.

In the case of any complications the surgeon is then asked to specify the complication.

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.

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.

The data relating to the endpoints of physical rehabilitation, or additional or corrective procedure, related to the replaced joint up to Week 24 will be derived from an ongoing clinical review of the concomitant non-drug treatment/procedure case report form (CRF) page. This review will identify treatments that are relevant for these endpoints, and a log of such data will be maintained. The data relating to the endpoint of concomitant analgesic medication use will be derived from an ongoing review of the concomitant analgesic drug CRF page. These reviews will be made during the study and data will be finalized prior to the database release for this study.

Events identified as the first symptom leading to total joint replacement will be reviewed and determined prior to the unblinding for the respective parent study.

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. The list of post-surgical complications will be developed during Study A4091064 and finalized prior to Study A4091058 unblinding. Other adverse events may be identified as post-surgical complications after the unblinding of the Study A4091058 database. These events will also be summarized as complications, and will be noted as having been included in the list after the unblinding of the Study A4091058 database.

Adverse Events which are “treatment emergent” in relation to the Baseline study day will be reported overall and by prior study treatment group. Adverse events ongoing from the parent study will continue to be followed in this study. They will not be included in incidence tables from this study unless the severity worsens.

Groups of the adverse events of abnormal peripheral sensation, sympathetic nervous system and decreased sympathetic function are shown below. These events will be evaluated from overall adverse events summaries if needed.

The preferred terms for adverse events of abnormal peripheral sensation are defined below.

Allodynia	Neuralgia
Axonal neuropathy	Neuritis
Burning sensation	Neuropathy, peripheral
Decreased Vibratory Sense	Paraesthesia
Demyelinating polyneuropathy	Paraesthesia oral
Dysaesthesia	Peripheral sensorimotor neuropathy
Formication	Peripheral sensory neuropathy
Hyperaesthesia	Polyneuropathy
Hyperpathia	Polyneuropathy chronic
Hypoaesthesia	Sensory disturbance
	Sensory loss
Hypoaesthesia oral	Thermohypoaesthesia
Intercostal neuralgia	Carpal tunnel syndrome
Sciatica	Tarsal tunnel syndrome

The preferred terms for adverse events of the sympathetic nervous system are defined below.

Abdominal discomfort	Micturition urgency
Anhidrosis	Nausea
Blood pressure orthostatic decreased	Nocturia
Bradycardia	Orthostatic hypotension
Diarrhea	Presyncope
Dizziness postural	Respiratory distress
Early satiety	Respiratory failure
Ejaculation delay	Sinus bradycardia
Ejaculation disorder	Syncope
Ejaculation failure	
	Urinary hesitation
Heart rate decreased	Urinary incontinence
Hypertonic bladder	Vomiting
Hypohidrosis	Anal incontinence
Pollakiuria	

The preferred terms for adverse events of decreased sympathetic function are defined below.

Anhidrosis	Orthostatic hypotension
Bradycardia	Syncope
Hypohidrosis	

Case Report Forms are available in Study A4091064 to capture results from neurological consultations or sympathetic nervous system consultations. If any such consultations occur, they will be reported overall and by prior study treatment group, as possible.

6.2. Other Endpoints

6.2.1. PK Endpoints

There are no PK endpoints in this study.

6.2.2. PD Endpoints

There are no PD endpoints in this study.

6.2.3. Outcomes Research Endpoints

There are no Outcomes Research endpoints in this study.

6.3. Covariates

There are no statistical models that will be fitted for the data in this study, and so there are no definitions of covariates.

Data will be summarized by parent study.

7. HANDLING OF MISSING VALUES

Data will be reported based on observed findings. No data will be imputed except as described next. Where a Week 24 summary is shown, it will relate to observed data collected at the Week 24/Early Termination visit and within the Week 24 window defined in Appendix 1.1. Additionally, data for the last observation carried forward (LOCF) will be presented for Week 24. This data can be thought of as a type of LOCF assessment, where the investigator has brought forward subject assessment from the point of early termination to the Week 24/Early Termination visit.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

8.1.1. Analyses for Continuous Data

Continuous endpoints will be summarized using the following statistics: number of subjects, arithmetic mean, standard deviation, median, minimum, and maximum values. These statistics will be shown by treatment group and overall.

8.1.2. Analyses for Categorical Data

Categorical data will be summarized by parent study and treatment group.

8.1.3. Analyses for Binary Endpoints

The incidence of subjects with total joint replacement and specific adjudication outcomes (listed below) will be summarized for all combined osteoarthritis studies. This incidence are shown by treatment group (with a tanezumab combined group, and a total for that parent study). The events to be analyzed are:

- Total Joint Replacement.
- Total Joint Replacement, with outcome adjudicated as:
    - Any of Rapidly Progressive Osteoarthritis (RPOA) type 1 or 2, Subchondral insufficiency fracture (SIF), Primary Osteonecrosis (ON), Pathological Fracture;
    - Any of RPOA type 2, SIF, Primary Osteonecrosis, Pathological Fracture;
    - RPOA type 1 or 2;
    - RPOA type 1;
    - RPOA type 2;
    - ON;
    - Pathological Fracture;
    - SIF;
    - Not enough information to determine rapid or Normal Progression of OA;
    - Normal Progression of OA;
    - Other Joint Outcome.

The analysis will show the number of subjects with the event, the number of subjects in the parent study treatment group (using the 'Safety Analysis Set'),

An overall summary of subjects with events (total joint replacement and then by adjudication outcome) for all combined osteoarthritis studies and by study will be shown, overall and by treatment group. In addition, two types of summarization, subject level with primary outcome and joint level, will be prepared for adjudicated outcome.

8.2. Statistical Analyses

8.2.1. Analysis of Endpoints

All subjects enrolled in the study who have a qualified *total joint replacement will be included in the summary tables.* In addition, three types of endpoints, the surgeon's assessment of procedural difficulty, the subject's overall satisfaction, and concomitant

nondrug treatment, will be summarized for subjects who were adjudicated with RPOA (type 1 and 2), RPOA (type 1), RPOA (type 2), Primary ON, SIF, or NPOA.

The events considered in the incidence of event summary are total joint replacement and total joint replacement with specific individual or grouped adjudication outcomes, as defined in Section 8.1.3.

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 (if needed)*, 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 (mean of the 4 items) *will be* summarized *by surgery type (hip, knee or shoulder)* and overall. *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).*

The total satisfaction score will be summarized using the mean (with standard deviation), median, and minimum and maximum values. These results will be shown by visit, with Week 24 (LOCF).

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 this *assessment, change from Baseline summary data are not relevant and will not be presented.* This summary will be shown separately for total joint replacements of the hip, knee and shoulder, as well as shown overall. These summaries will be shown for any post-surgery timepoint. *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).*

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 non-drug treatment/procedure. It *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. The list of post-surgical complications will be developed during Study A4091064 and finalized prior to Study A4091058* unblinding. Other adverse events may be identified as post-surgical complications after the unblinding of the Study A4091058 database. These events will also be summarized as complications, and will be noted as having been included in the list after the unblinding of the Study A4091058 database.

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.

Separate adverse event summaries by parent study treatment group for adverse events of abnormal peripheral sensation, and sympathetic nervous system will be presented. Adverse event summaries of *decreased sympathetic function* may *be presented.*

8.2.2. Summary of Analyses

Endpoint	Time points	Analysis Set	Statistical Method	Model/ Covariates/ Strata	Missing Data	Objective
Summary of total joint replacement (TJR) and adjudication outcomes (Joint Level)	Any time during parent study or 1064	SAS	None	N/A	Observed	Summary of frequency and the proportion
Summary of detail of adjudication outcomes (Joint Level)	Any time during parent study or 1064	SAS	None	N/A	Observed	Summary of frequency and the proportion
Summary of total joint replacement (TJR) and adjudication outcomes (Subject Level)	Any time during parent study or 1064	SAS	None	N/A	Observed	Summary of frequency and the proportion
Summary of detail of adjudication outcomes (Subject Level)	Any time during parent study or 1064	SAS	None	N/A	Observed	Summary of frequency and the proportion
Surgeon's assessment of procedural difficulty by TJR joint and total (All OA parent studies)	Assessed after surgery	SAS	None	N/A	Observed	Summary of surgical outcome
Subject's overall satisfaction with surgery by TJR joint and Total (All OA parent studies)	Week 4, 12, 24	SAS	None	N/A	Observed	% and frequency of each category
Subject's overall satisfaction with surgery by TJR joint and Total (All OA parent studies)	Week 4, 12, 24 and 24 (LOCF)	SAS	None	N/A	Observed (LOCF for Week 24 (LOCF))	Summary of surgical outcome
Physical rehabilitation in relation to replaced joint by TJR joint and Total (All OA parent studies)	Any time post-surgery	SAS	None	N/A	Observed	Summary of surgical outcome
Additional or corrective procedures relating to TJR by TJR joint and Total (All OA parent studies)	Any time post-surgery	SAS	None	N/A	Observed	

Endpoint	Time points	Analysis Set	Statistical Method	Model/ Covariates/ Strata	Missing Data	Objective
Average Pain in the joint to be replaced/replaced joint by visit and change from BL by TJR joint and Total (All OA parent studies)	BL, Week 4, 12, 24, 24 (LOCF)	SAS	None	N/A	Observed (LOCF for Week 24 (LOCF))	Summary of surgical outcome
WOMAC Pain, Physical Function and Stiffness subscales by visit and change from BL by TJR joint [Hip/Knee] and Total (All OA parent studies)	BL, Week 4, 12, 24, 24 (LOCF)	SAS	None	N/A	Observed (LOCF for Week 24 (LOCF))	Summary of surgical outcome
SPADI dimensions and total by visit and change from BL (All OA parent studies)	BL, Week 4, 12, 24, 24 (LOCF)	SAS	None	N/A	Observed (LOCF for Week 24 (LOCF))	Summary of surgical outcome
Post-surgical complications (All OA parent studies)	Any time post-surgery	SAS	None	N/A	Observed	
Concomitant analgesic medication use (All OA parent studies)	Any time post-surgery	SAS	None	N/A	Observed	Summary of surgical outcome
Subpopulation summary of Surgeon's Assessment of Procedural Difficulty for subjects who had RPOA (type 1 and type2), RPOA (type 1), RPOA (type 2), primary ON, SIF, or NPOA	BL, Week 4, 12, 24, 24 (LOCF)	SAS	None	N/A	Observed	Subgroup presentation
Subpopulation summary of Subject's Overall Satisfaction for subjects who had RPOA (type 1 and type2), RPOA (type 1), RPOA (type 2), primary ON, SIF, or NPOA	BL, Week 4, 12, 24, 24 (LOCF)	SAS	None	N/A	Observed	Subgroup presentation

Endpoint	Time points	Analysis Set	Statistical Method	Model/ Covariates/ Strata	Missing Data	Objective
Subpopulation summary of concomitant nondrug treatment for subjects who had RPOA (type 1 and type2), RPOA (type 1), RPOA (type 2), primary ON, SIF, or NPOA	Any time post-surgery	SAS	None	N/A	Observed	Subgroup presentation

SAS: Safety analysis set for subjects with TJR and entered into 1064

9. REFERENCES

N/A.

10. APPENDICES

Appendix 1. DATA DERIVATION DETAILS

Appendix 1.1. Definition and Use of Visit Windows in Reporting

Study visits/telephone contacts are planned at Baseline, Day of Surgery (Day 1, with assessments made by the surgeon within 10 days after the date of surgery), and Weeks 4, 8, 12, 16, 20 and 24. Information relating to the post-operative outcome measures is collected at Weeks 4, 12 and 24, and it is for these visits that windows will be defined. If a subject discontinues from the trial then the Week 24/Early termination visit assessments will be completed.

When multiple observations occur in a visit window, the observation closest to the protocol specified target day will be used, noting that the latter will be used in the case of a tie.

Visit	Target Study Day	Window
Baseline	Variable	[No lower limit, Day -1]
Day of Surgery	1	N/A
Week 4	29	[2,57]
Week 12	85	[58,127]
Week 24	169	[128, No upper limit]

Appendix 2. UNBLINDING PLAN

1. Introduction

The A4091064 is the long-term observational study without dosing to follow up subjects who undergo total joint replacement (TJR) of knee, hip or shoulder from one of parent studies (A4091056, A4091057, or A4091058) or sub-studies (A4091059, A4091061, or A4091063), and one of the secondary objectives is to compare the post-operative outcomes for tanezumab 2.5mg and 5 mg versus NSAIDs for subjects who underwent a TJR in A4091058.

The purpose of this unblinding plan is to describe who can access to the unblinding information of parent phase 3 studies (and sub-studies) while A4091064 is ongoing and the rationale. The goal is to maintain the double blind (subjects and investigator) at any study sites and among operational colleagues interacting with site directly about patient data in order to minimize the potential to introduce bias for comparison of the post-operative outcomes.

2. Rationale for Unblinding of Parent Phase 3 Studies to A4091064 Study Team Members

The rationale for the appropriateness of this approach for unblinding includes the following:

- Major endpoints to evaluate TJR follow-up of A4091064 are based on patient and/or surgeon reported outcomes, and an investigator or Pfizer study team will not evaluate them.

- All endpoints of A4091064 will be summarized descriptively and there is no formal hypothesis testing.

- A4091064 is a study being incorporated into the data package for regulatory submission. Pfizer team needs to evaluate TJR based on the data of both A4091064 and these parent studies (and sub-studies) simultaneously with considering these relationships by representatives who are familiar with these studies.

- No changes will be made to A4091064 study designs, conduct, or analysis based on the parent phase 3 studies unless the program is terminated or otherwise modified for safety findings, in which case, the changes would be reflected in a protocol amendment.

3. Unblinding Prior to Database Release of any Parent Phase 3 Studies

The phase 3 program is using a safety monitoring committee (SMC), which will have access to unblinded data throughout the parent phase 3 studies for the monitoring of subject safety. A separate SMC charter specifies the role and responsibilities of the SMC and the contact individuals within the Pfizer's organization and the SMC responsible for communication between these organizations.

4. At or after Database Release of any Parent Phase 3 Studies

This section describes who remains blind and who will become unblinded at or after database release of any parent phase 3 studies for A4091064 evaluation. The process of unblinding follows the following standard of procedure:

- Pfizer: DMB08 (Study Data Set Review, Release, and Archive)

4.1 Unblinded at or after Database Release

Following database release for phase 3 parent studies, unblinding of each parent study (and sub-studies) will occur at the individual subject level as well as at the summary (ie, treatment group) level to the A4091064 team members who are NOT defined as colleagues who remain blind in the section 4.2.

4.2 Blinded until Database Release of final phase 3 study

At the time of database release/unblinding for reporting of each parent study, Pfizer/Syneos/EPS roles of A4091064 study in below lists are to remain blinded of individual subject level in order to maintain the integrity of the blinding to subjects and investigators;

- Pfizer: Clinician interacting with site directly for TJR evaluation, and regional clinical site lead (RCSL);

- Syneos/EPS(Japan Local CRO): Clinical research associate, monitoring lead, CTA, and CMPL.

An investigator site (investigators, and all other site staff) participating in A4091064 is to remain blinded to individual subject treatment assignment until all subjects in the site will be finished A4091064 and until all data for these subjects will be cleaned.

Pfizer SOPs CT20 (Public Disclosure of Pfizer Clinical Study Data and Authorship) and DMB10 (Clinical Study Report) require unblinded results to be provided to study sites after the trial has completed. Some amendment/deviation may be applied to delay sending results from the parent studies or sub-studies until a site has completed participation of all subjects in the site of A4091064.

Selected investigators may be required to review an interim CSR for A4091064 in order to sign the Investigator's Declaration. In order to minimize any potential bias after unblinding of any parent study, an investigator will be selected who would not have any on-going A4091064 subjects at the time of the investigator's review of an interim A4091064 CSR.

It is also recognized that unblinded summary results may become publicly known through press release, presentations at scientific conference, publication and so on.