STATISTICAL ANALYSIS PLAN
VERSION: FINAL

Clinical Study Protocol Title:	**A Phase 3 Randomized, Double-Blind, Multi-Dose, Placebo-Controlled Study to Evaluate the Long-Term Safety and the Efficacy of Fasinumab in patients with pain due to Osteoarthritis of the Knee or Hip**
Compound:	**REGN475**
Protocol Number:	**R475-PN-1523**
Sponsor:	**Regeneron Pharmaceuticals, Inc.**
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The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AA	Adjudicated arthropathy
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine Aminotransferase
ARGUS	Pharmacovigilance and clinical safety software system
AST	Aspartate Aminotransferase
C_{max}	Maximum observed drug concentration
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
C_{trough}	Concentration measured at the end of a dosing interval at steady state (taken directly before next administration)
DA	Destructive arthropathy
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
EOS	End of study
EOT	End of treatment
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
hs-CRP	High-sensitivity C-reactive protein
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IVRS	Interactive voice response system
JR	Joint replacement
K-L	Kellgren-Lawrence
LDH	Lactate dehydrogenase

LTS	Long-term safety
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model repeated measure
MRI	Magnetic resonance imaging
NGF	Nerve growth factor
NRS	Numeric Rating Scale
NSAIDs	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
OMERACT-OARSI	Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative and The Outcome Measure in Rheumatology
PCSV	Potentially clinically significant value
PK	Pharmacokinetic
PPS	Per protocol set
PT	Preferred term
Q4W	Every 4 weeks
Q8W	Every 8 weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse event
TIA	Transient ischemic attack
TrkA	Tyrosine kinase type 1
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Women of childbearing potential
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

1. OVERVIEW

The purpose of the Statistical Analysis Plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study data prior to database lock. The SAP is intended to be a comprehensive and detailed description of the definitions and statistical methods to be used in the analysis of data for study R475-PN-1523.

This plan may be revised during the study to accommodate protocol amendments and/or to make changes to adapt to unexpected issues in study execution and/or data that affect planned analyses. These revisions will be based on blinded review of the study and data, and a final plan will be issued prior to the first step database lock and before unblinding of the study.

1.1. Background/Rationale

This is a Phase 3, randomized, double-blind, placebo-controlled study designed to evaluate the long-term safety, tolerability, and the efficacy of fasinumab in patients with pain due to radiographically confirmed OA of the knee or hip who have a history of inadequate pain relief with paracetamol/acetaminophen, and a history of inadequate pain relief or intolerance to oral NSAIDs, and opioid therapy. During the initial 16 weeks of the trial, standard-of-care pain medications will be prohibited with the exception of paracetamol/acetaminophen, which will be provided as a rescue medication, and low-dose aspirin for cardiac prophylaxis. Following the first 16 weeks, patients will be able to utilize standard-of-care pain medication including limited use NSAIDs (for non-OA pain or fever), as well as paracetamol/acetaminophen, in addition to study drug. Therefore, this study will also provide safety data on the concomitant use of fasinumab with other analgesics, including limited use NSAIDs.

A subset of patients will participate in an efficacy sub-study, in addition to participation in the main long-term safety study. In the sub-study, efficacy parameters will be assessed over the 16 weeks following randomization to a treatment group. Details on dosing regimen and allocation ratios across amendments for both the main study and efficacy sub-study are provided in Section 2.1.

There have been several modifications to the dosing regimens for the study. Patients initially randomized to the 6 mg or 9 mg Q4W dosing regimen or matching placebo under the original protocol and amendments 1 and 2 were discontinued from study medication on 30December 2016 per US FDA request. The patients were encouraged to otherwise continue all protocol visits and complete all study procedures with the exception of receiving study medication. Under amendments 3 and 4, main study patients were randomized to 6 mg Q8W or matching placebo. Under amendment 5 global (Issued 16March 2017) or later amendments, main study patients were randomized to 6 mg fasinumab Q8W, 3 mg fasinumab Q4W, 1 mg Fasinumab Q4W, or matching placebo. Efficacy sub-study patients were randomized to 6 mg fasinumab Q8W, 3 mg fasinumab Q4W, 1 mg fasinumab Q4W, 1 mg fasinumab Q8W, or matching placebo Q4W. Patients randomized to efficacy sub-study will continue in the main study on randomized treatment after participation in the efficacy sub-study. Prior to amendment 5 global all subjects participated only in the main study. Enrollment for the main study under

amendment 5 or later was paused on 3January 2017 not due to any safety concern, but to hold enrollment of 6 mg Q8W vs placebo until further discussion with health authorities on safety database requirement. The efficacy sub-study has completed enrollment as of 7 February 2018.

The Data Monitoring Committee recommended that the 3mg Q4W and 6mg Q8W doses be discontinued due to safety concerns. A decision was made by the Sponsor to conduct an unplanned interim safety analysis of the data to corroborate these findings. Based on the IDMC recommendation and the totality of evidence to date with regards to safety, only the 1mg Q4W, 1mg Q8W doses and placebo arms would be carried forward in the study. The 3 mg Q4W and 6Mg Q8W doses were discontinued from further dosing; however, subjects have been encouraged to remain in the study and will be followed for all study visits until completion of the end of study visit in order to continue to monitor for safety and to allow complete data collection.

The Abridged Unblinded DMC Interim Report was made available to members of the study team including the study biostatistician and study medical director. This abridged DMC report included the following subject level listings:

- Listing of Serious of Adverse Events from the Case Report Form (amendment 3)
- Listing of Serious of Adverse Events from the Case Report Form (amendment 5 sub-study)
- Listing of Deaths (amendment 3)
- Listing of Adjudication Results for Subjects with Arthropathies (amendment 3)
- Listing of Adjudication Results for Subjects with Arthropathies (amendment 5 Sub-study), Listing of Subjects with Total Joint Replacement (amendment 3)
- Listing of Subjects with Total Joint Replacement (amendment 5 Sub-study)

Restricted to subjects randomized to Placebo SC Q4W or Q8W (amendments 3 or earlier), 6 mg SC Q4W or Q8W (amendments 3 or earlier), Placebo SC Q4W (amendment 5 sub-study), 3 mg SC Q4W (amendment 5 sub-study), 6 mg SC Q8W (amendment 5 sub-study). This report did not contain any information on the 1mg Q4W and 1mg Q8W doses or their placebo arms that are being carried forward; hence there is no risk of unblinding of the blinded study team members to doses being continued. Continued monitoring of all subjects not being dosed also remains blinded to the clinical team as to treatment received.

Given the discontinuation of the 3 mg and 6 mg doses, greater exposure to the fasinumab 1 mg dose was required to increase the size of the fasinumab safety database for potentially clinically relevant doses. Therefore, under amendment 8, patients will be randomized in a 3:3:1 ratio to fasinumab 1 mg Q8W, 1 mg Q4W or placebo. This randomization ratio was chosen based on the need to enroll more patients on the 1 mg dose regimens and the need to include placebo patients for blinding purposes.

Supportive trials include data from 2 completed fasinumab phase 1 studies in healthy volunteers (R475-PN-0817 and TD-11480), as well as data from the completed fasinumab phase 2 proof-of-concept study in patients with pain due to OA of the knee (R475-PN-0901), and results from the phase 2 study in patients with osteoarthritis of the hip or knee (R475-PN-1227).

1.2. Study Objectives

1.2.1. Primary Objectives

The primary objective of the study is to describe the safety and tolerability of fasinumab, including Adverse events of special interest (AESIs), in patients with pain due to radiographically-confirmed OA of the knee or hip.

1.2.2. Exploratory Objectives

Other objectives of the study are:

- To assess the use of paracetamol/acetaminophen for the fasinumab arms compared to placebo from baseline to week 16
- To assess the use of paracetamol/acetaminophen for the fasinumab arms compared to placebo from baseline to week 52
- To assess the use of standard-of-care analgesic medication, including NSAIDs, for non-OA pain in patients randomized to fasinumab compared to placebo from week 16 through the end of treatment
- To assess time to JR

1.2.3. Additional Objectives for the Efficacy sub-study

The objective of the stub-study is to evaluate the efficacy of fasinumab compared with placebo when administered to patients with pain due to radiographically-confirmed OA of the knee or hip.

1.2.4. Modifications from the Statistical Section in the Final Protocol

The following exploratory endpoint is in the protocol but will not be included in the analysis plan since there is no definitive literature or guideline on the criteria for needing joint replacement:

- Incidence of and time to cases meeting pre-specified criteria for needing joint replacement.

The following exploratory endpoints are not listed in the protocol but are included in the analysis plan:

- Time to Adjudicated Arthropathy (AA), time to Destructive Arthropathy (DA)

The following lab safety endpoint is not listed in the protocol but is included in the analysis plan:

- High-sensitivity C-reactive protein (hs-CRP)

1.2.5. Revision History for SAP Amendments

The language of Section 7"Timing of Statistical Analysis" was updated to clarify that the week 72 analysis is not the final analyses. Section 8 "Interim Analyses" was updated to clarify when interim analyses may be performed.

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

This is a Phase 3, randomized, double-blind, multi-dose, placebo-controlled study to evaluate the long-term safety and efficacy of fasinumab in patients with pain due to osteoarthritis of the knee or hip. Patients are randomized into either the main study or the efficacy sub-study. After the 16-week sub-study, efficacy sub-study patients continue on the randomized treatment as part of the Long-Term Safety (LTS) study in which dosing will continue through week 48. The LTS study is made up of both main study patients and efficacy sub-study patients.

There have been several modifications to the randomization scheme for both the main study and the efficacy sub-study as follows:

- Original Protocol, Amendment 1 & 2

  Under the original protocol and amendments 1 and 2, main study patients were randomized to 6 mg or 9 mg Q4W or matching placebo in a 2:2:1 ratio. Efficacy sub-study patients were to be randomized to 6 mg or 9 mg Q4W or matching placebo in a 1:1:1 ratio. Patients randomized to these earlier versions of the protocol with the 6 mg or 9 mg Q4W dosing regimen or matching placebo were discontinued from study medication but encouraged to otherwise continue all protocol visits and complete all study procedures with the exception of receiving study medication. Efficacy sub-study enrollment did not start under the original protocol and amendment 1 and 2.

- Amendment 3 & 4

  Under amendment 3 and 4, main study patients were randomized to 6 mg Q8W or matching placebo in a 2:1 ratio. Efficacy sub-study patients were to be randomized to 6 mg Q8W or matching placebo in a 1:1 ratio. However, there were patients enrolled into the efficacy sub-study under amendment 3 and 4.

- Amendment 5 and 6

  Under amendment 5 global or later, main study patients were to be randomized to 6mg fasinumab Q8W, 3 mg fasinumab Q4W, 1 mg Fasinumab Q4W, or matching placebo Q4W in a 1:2:2:1 ratio. However, there were no patients enrolled into the main safety study under amendment 5 or amendment 6. Efficacy sub-study patients were randomized to 6 mg fasinumab Q8W, 3 mg fasinumab Q4W, 1 mg fasinumab Q4W, 1 mg fasinumab Q8W, or matching placebo Q4W in a 1:1:1:1:1 ratio. Efficacy sub-study has completed enrollment as of 7 February 2018.

Due to the recommendation of the Independent Data Monitoring Committee, the 3mg Q4W and 6mg Q8W doses have been discontinued as described above. This SAP will apply to the amended protocol reflecting the most recent change in doses recommended by the IDMC, now including only the 1 mg Q4W and 1mg Q8W doses and placebo arms.

- Amendment 7 (urgent safety measure)

  Issued on 24 May 2018, all patients previously randomized to 3 mg Q4W or 6 mg Q8W under earlier versions of the protocol will be were discontinued from study drug but encouraged to otherwise complete all remaining study visits and study procedures in the follow-up period, and the end of study phone call. Anyone previously randomized to 9 mg Q4W or 6 mg Q4W (or matching placebo) before amendment 3, or randomized to 6 mg Q8W or 3 mg Q4W under amendment 3 or subsequent amendments, was discontinued from study drug and encouraged to complete all remaining study visits and study procedures in the follow up period and the end of study phone call.

- Amendment 8

  Under amendment 8, patients will be enrolled into the main safety study. They will be randomized in a 3:3:1 ratio of fasinumab 1 mg Q8W, 1 mg Q4W or placebo. Patients randomized to 1 mg Q8W will receive alternating placebo injections at the monthly visits where active study medication drug will not be given to maintain the blind.

Stratification for the main study and the efficacy sub-study are as follows:

Main study stratification

- Randomization is stratified by screening K-L score (2-3, 4) and by geographic region (North America, Latin America, Europe, or Asia/Pacific/South Africa).

Efficacy sub-study stratification

- Randomization is stratified by screening K-L score (2-3, 4), geographic region (North America, Latin America, Europe, or Asia/Pacific), and by index joint.

2.2. Sample Size and Power Considerations

Long Term Safety study

The sample size for this long-term safety study was selected according to regulatory requirements for sufficient patients with adequate treatment exposure. With approximately 1750 patients expected to be treated with placebo, a total of up to 7000 patients was planned to be randomized. This study will provide an adequate assessment of safety in patients with pain associated with OA. For example, based on Exact Binomial Testing, with approximately 5250 patients with pain

associated with OA exposed to fasinumab, if the observed incidence rate of is 1.0%, one can be 97.5% confident that the true incidence rate is not greater than 1.3% (Table 1).

Departures from planned sample sizes will be described in the CSR.

Table 1: Observed Incidence Rate (n/N) and 95% CI (Based on Exact Binomial Test) (%)

	2-sided 95% CI
Observed Incidence Rate	**All fasinumab combined (N=5250)**
0.5%	(0.32%, 0.72%)
1%	(0.74%, 1.30%)
2%	(1.64%, 2.42%)
3%	(2.56%, 3.51%)
4%	(3.49%, 4.57%)
5%	(4.42%, 5.61%)

Efficacy Sub-study

The sample size of the efficacy sub-study was selected to have a sufficient number of patients to allow treatment comparisons of primary efficacy endpoints. The effect size for WOMAC pain subscale score, WOMAC physical function subscale score and Patient Global Assessment were 0.46, 0.46, and 0.36, respectively, as observed in the phase 2 study R475-PN-1227. To maintain the overall significance level of 0.05, the sequential multiple test procedure as described in Section 5.6.1 is applied to the hypothesis tests for the primary and secondary endpoints. Assuming a dropout rate of 15% at week 16, with 200 patients per treatment arm, there will be at least 96% power to detect an effect size of 0.46 for WOMAC pain and physical function subscale scores based on a 2-sided test at the 0.0167 significance level. This sample size will provide at least 82% power to detect an effect size of 0.36 for Patient Global Assessment score.

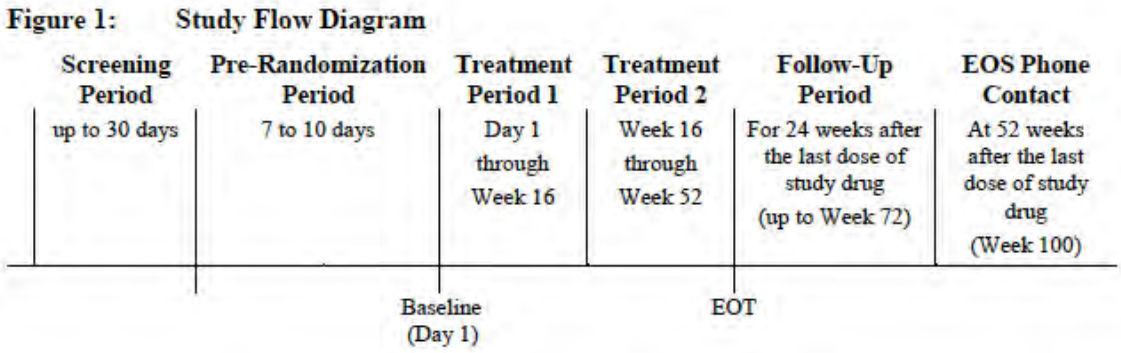
2.3. Study Plan

Study Visits

The study consists of a screening period of up to 30 days (Screening Period), followed by a 7 to 10 day pre-randomization period (Pre-Randomization Period), a 16-week randomized, double-blind, placebo-controlled treatment period (Treatment Period 1), a 36-week, double-blind, placebo-controlled treatment period (Treatment Period 2) in which non-NSAID standard-of-care pain medications can also be used in the event of inadequate pain relief for OA pain, a 24-week follow-up period, and an end of study phone contact at 52 weeks following the last dose of study drug to determine whether a joint replacement (JR) has been conducted or is scheduled (or the patient is on a waiting list).

A subset of patients will also be participating in a 16-week efficacy sub-study to characterize the efficacy of fasinumab. Efficacy assessments will be performed during treatment period 1, which will be followed by the 36-week treatment period 2, and a 24-week follow-up period. See Figure 1 for the Study Flow Diagram.

Figure 1: Study Flow Diagram



The Schedule of Events table is presented in Appendix 11.1.

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (1998), the following populations will be used for all statistical analyses:

3.1. Full Analysis Set (FAS)

Efficacy sub-study

The full analysis set for the efficacy sub-study (FAS-substudy) includes all randomized patients in the efficacy sub-study. Efficacy analyses are based on the treatment allocated (as randomized).

LTS study

The full analysis set for the LTS study (FAS-LTS) includes all randomized patients in the overall study (randomized within either the efficacy sub-study or the main study). This analysis set will be used to summarize baseline characteristics and patient disposition; it is based on the treatment allocated (as randomized).

3.2. The Safety Analysis Set (SAF)

Efficacy sub-study

The safety analysis set for the efficacy sub-study (SAF-substudy) includes all randomized patients in the efficacy sub-study who received any study drug during the efficacy sub-study; it is based on the treatment received (as treated). Patients who receive at least one dose of fasinumab will be classified to the respective active treatment arm for the purpose of the analysis. Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF-sub-study for the efficacy sub-study.

LTS study

The safety analysis set for the LTS study (SAF-LTS) includes all randomized patients in the overall study (randomized within either the efficacy sub-study or the main study) who received any study drug during the LTS study; it is based on the treatment-as-received (as treated). Patients who receive at least one dose of active fasinumab will be classified to the respective active treatment arm for the purpose of the analysis. Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF for the entire study.

3.3. Per Protocol Set

Efficacy sub-study

PPS will include all FAS-sub-study patients who do not have major protocol deviations through week 16. The PPS will be used to perform sensitivity analyses for the primary and key secondary endpoints. Patients with the following major protocol deviations will be excluded from the PPS:

- Intolerance or Inadequate pain relief with analgesics assessment was not performed
- Analgesic medications administered during the week 16 treatment period prohibited by protocol
- Confirmed treatment unblinding that occurred in error.
- Study drug administered without a randomization record per IVR.
- Randomization without documented study eligibility

3.4. The Pharmacokinetic Analysis Set

The PK analysis set includes all treated patients who received any study drug and who had at least 1 non-missing drug concentration following the first dose of study drug.

3.5. The Anti-drug antibody Analysis Set

The ADA analysis set includes all treated patients who received any treatment and who had at least 1 non-missing post-dose ADA result.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (e.g., age, sex, race, ethnicity, weight, height, etc.), disease characteristics including index joint, Kellgren-Lawrence score, WOMAC pain subscale score at screening, medical history, and medication history for each patient.

The following demographic and baseline characteristic variables will be summarized by treatment group:

- Age at screening (years)
- Age category (<65, >=65 years)
- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White, and Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported)
- Baseline Weight(kg)
- Baseline Height(cm)
- Baseline Body mass index (BMI) calculated from weight and height
- Index Joint (Knee or Hip)
- K-L score for the Index Joint
- WOMAC pain score of the index joint at screening
- Duration of OA at baseline
- History of analgesic intolerance and inadequate pain relief

Additional baseline characteristics will be summarized if needed.

4.2. Medical History

Medical history will be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to the latest available version of Medical Dictionary for Regulatory Activities (MedDRA®).

4.3. Prior/Concomitant Medications and Procedures, Prohibited Medication

Medications/Procedures will be recorded from the day of informed consent until the End of Follow-up Clinic Visit. Medications will be coded to the Anatomical Therapeutic Chemical (ATC) level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of WHO Drug Dictionary (WHODD). Patients will be counted once in all ATC categories linked to the medication.

Medication/Procedure Classifications

Prior medications/procedures are defined as medications/procedures starting prior to the first dose of study drug.

Concomitant medications/procedures are defined as medications/procedures starting prior to or during each respective on-treatment period (as defined in Section 5.8) and ending during or after the respective on-treatment period.

Post treatment medications/procedures are medications/procedures starting after the on-treatment period (as defined in Section 5.8).

Prohibited Medication

Patients were required to discontinue all non-study pain medication (oral or topical; except up to 150 mg/day of aspirin/5-ASA, which is permitted for cardiac prophylaxis, per local guidelines) and opioid analgesic medications, starting at the pre-randomization phone call/visit.

Analgesic medications (including tramadol) were prohibited through week 16. Patients were directed not to take concomitant medications that contain NSAIDs (oral or topical, except up to 150 mg/day of aspirin/5-ASA, which is permitted for cardiac prophylaxis) during treatment period 1. Patients could have taken non-NSAID standard-of-care therapy in addition to study drug, in the event of inadequate pain relief for OA pain, starting after the week 16 visit. Though use of oral NSAIDs should generally be avoided, a limited use is allowed after week 16 for non-OA related pain or fever after week 16. A list of medications containing NSAIDs will be provided in the study reference manual. The dose of oral NSAIDs may be increased and topical NSAIDs may be used during the follow-up period, but no earlier than 16 weeks after the last dose of study drug.

Other excluded drugs during treatment period 1 are:

- Medical marijuana
- Hyaluronic Acid Intra-articular Injections
- Cyclobenzaprine, carisoprodol, orphenadrine, tizanidine

For efficacy sub-study only during treatment period 1:

- Glucosamine sulfate
- Chondroitin sulfate

Other excluded drugs during both treatment periods 1 and 2 are:

- Any other investigational agent
- Corticosteroids (topical and inhaled formulations are permitted)
- Cyclosporine
- Azathioprine
- Tumor necrosis factor antagonists
- IL-1 inhibitors, including diacerein
- IL-6 or IL-6 receptor antagonists
- Abatacept

4.4. Efficacy Variables for the Efficacy sub-study

4.4.1. Primary Efficacy Variable(s)

The co-primary efficacy endpoints assessed for the efficacy sub-study only are:

- Change from baseline to week 16 in the WOMAC pain subscale score
- Change from baseline to week 16 in the WOMAC physical function subscale score

4.4.2. Key Secondary Efficacy Variable(s)

The key secondary efficacy endpoints assessed for the efficacy sub-study only are:

- Change from baseline to week 16 in the Patient Global Assessment for OA score
- Percentage of patients who had a response at week 16, with response defined as an improvement by ≥30% in WOMAC pain subscale score

4.4.3. Additional Secondary Efficacy Variable(s)

The additional secondary efficacy endpoints to be assessed in the efficacy sub-study only are:

- Change from baseline to week 16 in the average weekly walking index joint pain using the NRS pain scale

4.5. Safety Variables

Patient safety will be assessed through the collection of reported adverse events (AEs), clinical laboratory data, vital signs, ECG, Survey of Autonomic Symptoms Questionnaire, neurological exams and physical exams. Unless otherwise noted, the baseline value is defined as the last available value before the first dose of study drug.

Adverse events (AE) and Serious Adverse Events (SAE) will be collected from the time of informed consent signature and then at each visit until the End of Follow-up Clinic Visit. All AEs are to be coded to a "Preferred Term (PT)" and associated primary "System Organ Class SOC" according to the MedDRA® (the latest current available version).

An Adverse Event is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

A Serious Adverse Event is an adverse event (AE) that is classified as serious according to the criteria specified in the protocol.

Laboratory results, vital signs, or ECG abnormalities are to be recorded as AEs if they are medically relevant: symptomatic, requiring corrective therapy, leading to treatment discontinuation and/or fulfilling a seriousness criterion.

4.5.1. Primary Safety Variables

The primary safety endpoint in the study is safety monitoring including AE incidence, SAE, incidence, AESI incidence, changes in safety lab analyses, and incidence of anti-fasinumab antibody formation from baseline to week 52 (treatment period 1 and 2) and to week 72 (end of follow-up period).

More specifically, this includes:

- Incidence of adjudicated arthropathy events
- Incidence of destructive arthropathy events
- Incidence of JR (All JRs and AESI JRs) events – including endpoint for all JRs by the telephone survey approximately 52 weeks after the last dose of study drug
- Incidence of peripheral neurosensory AESI events

- Incidence of sympathetic nervous system dysfunction AESI events
- AE incidence, SAE incidence, changes from baseline in safety laboratory analyses, and incidence of anti-fasinumab antibody formation
- Change from baseline in minimum joint space width of the index joint (knee, hip)
- Incidence of confirmed orthostatic hypotension from baseline

The raw incidence rate is defined as the number of events divided by the duration of the observation period and presented as number of events per 100 patient-years.

4.5.2. Exploratory Safety Variables

Exploratory safety endpoints include:

- The proportion of patients taking rescue medication, number of days on rescue medication, and weekly average usage of rescue medication from baseline to week 16 and from baseline to week 52
- The percent of patients using standard-of-care analgesic medication from week 16 to week 52
- Time to joint replacement (JR) decision
- Survey of Autonomic Symptom scores from baseline to week 52 and from baseline to week 72
- Time to AA, time to DA

4.5.3. Adverse Events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate.

AESI are selected using e-CRF specific tick box on the AE page.

Events considered to be AESIs for the study are:

- Adjudicated arthropathy (as confirmed by adjudication)
- Sympathetic nervous system dysfunction (as diagnosed after consultation with an appropriate specialist, such as a neurologist and/or cardiologist)
- Peripheral sensory AEs that require a neurology or other specialty consultation

- JR surgery (AESI defined in Protocol Section 7.6.1.4 as elective JR surgery not due to new or worsening disease)

4.5.4. Laboratory Safety Variables

The clinical laboratory tests include blood chemistry, hematology, urinalysis, urine chemistries, hs-CRP, and others. Samples for laboratory testing will be collected at the time points specified in the Schedule of Events (Appendix 11.1). Clinical laboratory values will be in standard international (SI) units, including associated normal ranges provided by the central laboratory, and grouped by function in summary tables. Clinical laboratory values in conventional (US) units will also be available in the database, with associated normal ranges.

Both actual test values and "change from baseline" values (defined as the post-baseline value minus the baseline value) will be used in central lab result summaries. Potentially clinically significant values (PCSV) ranges will be applied to central lab test values as applicable (see Appendix 11.2 for PCSV definitions).

4.5.5. Biomarker variables

Biomarker analysis will be performed in a separate biomarker SAP.

4.5.6. Vital Signs

The following vital signs parameters will be collected at according to the Schedule of Events in Appendix 11.1:

- Body temperature (^{o}C)
- Sitting/supine/standing/orthostatic systolic and diastolic blood pressures (mmHg) and pulse (bpm)
- Respiratory rate (bpm)

Both actual values and "change from baseline" values (defined as the post-baseline value minus the baseline value) will be used in the result summaries. Potentially clinically significant values (PCSV) ranges will be applied to the vital sign parameter values as applicable (see Appendix 11.2 for PCSV definitions).

4.5.7. Orthostatic Hypotension

A patient will be determined to have orthostatic hypotension if any of the following criteria are met:

- If the supine blood pressure is <160 mmHg systolic, a decrease in either the 1 or 3 minute standing systolic blood pressure of ≥20 mmHg or a decrease in the standing diastolic blood pressure of ≥10 mmHg from the supine systolic or diastolic blood pressure

OR

- If the supine blood pressure is ≥160 mmHg systolic, a decrease in either the 1 or 3-minute standing systolic blood pressure of ≥30 mmHg or a decrease in the standing diastolic blood pressure of ≥15 mmHg from the supine systolic or diastolic blood pressure

OR

- An increase in either the 1 or 3-minute standing heart rate of ≥30 bpm from the supine heart rate

OR

- The patient is unable to stand for either one of the standing blood pressure measurements due to dizziness or lightheadedness

Confirmed orthostatic hypotension is defined as initial assessment meeting the above orthostatic hypotension criteria confirmed by subsequent repeated assessments per protocol or if initial assessment met the above orthostatic hypotension criteria yet repeated assessments were not performed.

4.5.8. 12-Lead Electrocardiography

A standard 12-lead ECG will be performed according to the Schedule of Events in Appendix 11.1 with the patient in the supine position for approximately 5 minutes and prior to blood samples being drawn. Heart rate will be recorded from the ventricular rate and the PR, QRS, and QT, QTc intervals, and ECG status (normal, abnormal not clinical significant or abnormal clinical significant) will also be recorded.

QTcF and QTcB are defined as follows:

QTcF (ms) $=QT/RR^{1/3}$ and QTcB (ms) $=QT/RR^{1/2}$,

where QT is the uncorrected QT interval measured in ms, and RR is 60/HR with HR being the heart rate in beats per minute.

Potentially clinically significant values (PCSV) ranges will be applied to the ECG parameter values as applicable (see Appendix 11.2 for PCSV definitions).

4.5.9. Physical and Neurological Examination Variables

Patients will have a physical examination including an examination of the knees, hips, and shoulders performed according to the Schedule of Events in Appendix 11.1. The result for each body system is an outcome of normal or abnormal. Neurological evaluations of specific domains as listed in the protocol will be described as normal or abnormal.

4.5.10. Other Safety Variables

- Joint Pain Questionnaire:
  - Number of subjects with significantly worse joint pain in any joint at each scheduled visit
  - Number of subjects with significantly worse joint pain by joint at each scheduled visit
- Joint space width for the index joints as well as other knee or hip joints at each scheduled visit
- Joint replacement:
  - number and percentage of patients with joint replacement (all JRs)
  - time to joint replacement decision (all JRs)

4.6. Pharmacokinetic Variables

The Pharmacokinetic (PK) variable will be fasinumab concentrations in serum at specified sampling time points.

4.7. Anti-Drug Antibody Variables

Samples for Anti-Drug Antibody (ADA) evaluation will be collected at baseline and at subsequent study visits.

Anti-drug antibody variables will include ADA status (positive or negative) and titer as follows:

- Total subjects negative in the ADA assay at all time points analyzed
- Pre-existing immunoreactivity - a positive ADA response at baseline with all post-dose ADA results negative, or a positive ADA response at baseline with all post-dose ADA responses less than 9-fold over baseline titer levels.
- Treatment emergent - defined as any post-dose positive ADA response when baseline results are negative
  - Persistent - A positive result in the ADA assay detected in at least 2 consecutive post baseline samples separated by at least a 16-week post baseline period [based on nominal sampling time], with no ADA-negative results in-between, regardless of any missing samples
  - Indeterminate - A positive result in the ADA assay at the last collection time point analyzed only, regardless of any missing samples

  - Transient - Not persistent or indeterminate regardless of any missing samples

- Treatment boosted - defined as any post-dose positive ADA response that is at least 9-fold over the baseline level when baseline is positive in the ADA assay

- Titer Values

- Titer category: low (titer <1,000); moderate (1,000≤ titer ≤10,000); high (titer >10,000)

- Neutralizing ADA activity for samples positive in the ADA assay

5. STATISTICAL METHODS

For continuous variables, descriptive statistics will include the following: the number of patients reflected in the calculation (n), mean, median, standard deviation (SD), minimum, maximum, and the first and third quartiles (Q1 and Q3).

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

5.1. Statistical Methods for Long-Term Safety Study

5.1.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be descriptively summarized by treatment group, combined fasinumab, and overall based on the FAS-LTS. Parameters to be summarized include those described in Section 4.1.

5.1.2. Medical History

Medical history will be descriptively summarized by treatment group, combined fasinumab and overall for the FAS-LTS. Summaries will show patient counts (percentages) by primary SOC and PT. The tables will be sorted by decreasing frequency of primary SOC in the overall group. Within each primary SOC, PTs will be sorted by decreasing frequency in the overall group.

5.1.3. Prior / Concomitant Medications

Prior Medications

All prior medications, dictionary coded by WHO, will be descriptively summarized by treatment group, and combined fasinumab based on the FAS-LTS. Summaries will present patient counts (and percentages) for all prior medications, by decreasing frequency of the overall group incidence of ATC followed by ATC level 2, ATC level 4 and preferred term. In case of equal frequency across anatomic or therapeutic categories, alphabetical order will be used. Patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication but may be counted several times for the same medication.

Concomitant Medications

All concomitant medications, dictionary coded by WHO, will be descriptively summarized by treatment group, and combined fasinumab based on the SAF-LTS. Summaries will present patient counts (and percentages) for the concomitant medication groups described in Section 4.3 for all concomitant medications, by decreasing frequency of the combined fasinumab group incidence of ATC followed by ATC level 2, ATC level 4 and preferred term. In case of equal frequency across anatomic or therapeutic categories, alphabetical order will be used. Patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication, hence may be counted several times for the same medication.

The following will be summarized:

- Prior Medications
- Concomitant medications
- Post-treatment medications
- On-study (Concomitant + Post-Treatment) Medications

When medication start/end date is missing, the rules for determining whether a medication is prior, concomitant, or post-treatment, are specified in Section 6.3.

5.1.4. Prohibited Medications

Number and percentage of patients with prohibited medications will be descriptively summarized by treatment group, and combined fasinumab based on the SAF-LTS. The tables will be sorted by decreasing frequency of ATC Level 2, ATC Level 4, and preferred term in the combined fasinumab group.

The number of patients with NSAID use during treatment period 1 will be summarized by treatment group, and combined fasinumab. Additionally, the number of patients with more than the limited amount of NSAID use during treatment period 2 will be summarized by treatment group, and combined fasinumab for patients in the SAF-LTS.

Total NSAIDs-use days during each treatment period and follow-up (before AA for patients with AA) will be summarized by treatment group, and combined fasinumab for patients in the SAF-LTS. Additionally, days from last study drug dose to first NSAID dose will be summarized by treatment group, and combined fasinumab for patients in the SAF-LTS.

5.1.5. Patient Disposition

The disposition of patients in the study will be summarized by treatment group, combined fasinumab and overall for FAS-LTS.

5.1.5.1. Screening Disposition

Percentages will be calculated using the number of screened patients as the denominator.

- Screened patients (defined as having signed the ICF).
- Patients randomized (defined in the protocol as having received a randomization number per IVRS).
- Patients did not meet inclusion/exclusion criteria but randomized (if applicable).
- Patients treated but not randomized (if applicable).

- Screen Fail patients. Reason for screen failure will be provided.

5.1.5.2. LTS study Disposition

- Unless otherwise noted, percentages will be calculated using the number of patients in FAS-LTS as the denominator. This will be summarized by treatment group, combined fasinumab, and overall for the LTS study. Kaplan-Meier plot of time to treatment discontinuation will be provided. Summaries will provide the frequency (and percentage as applicable) of patients that met the criteria for the following variables:

- Patients randomized (defined as having received a randomization number). This row will reflect grouping based on randomization assignment.

- Patients randomized but not treated. This row will reflect grouping based on randomization assignment.

- Patients randomized and treated.

- Patients who completed the study, patients who withdrew from the study and reason for study withdrawal.

- Patients who completed study treatment, patients who discontinued treatment and reason for treatment discontinuation.

5.1.5.3. Analysis Set

Summary of the number (and percentage) of patients in each analysis set) will be by treatment group, combined fasinumab, and overall for the LTS.

Additionally, the following listings will be provided (if applicable):

- Listing of Patients Treated but not Randomized.

- Listing of Patients Randomized but not Treated.

- Listing of Patients Randomized but not Treated with the Randomized treatment.

- Listing of Patient Disposition for all Randomized Patients.

- Listing of Screening Failures and reasons for all screen failed patients.

5.1.6. Extent of Study Treatment Exposure and Compliance

The analysis population for the entire LTS study is based on the SAF-LTS.

5.1.6.1. Measurement of Treatment Compliance

Compliance with protocol-defined investigational product will be calculated by treatment group and combined fasinumab as follows:

- (Number of actual injections of study drug during the LTS study exposure period) / (Number of planned injections of study drug during the LTS study exposure period on or before the time that the patient discontinues from the treatment phase of the study) x 100%

Treatment compliance will be presented by descriptive statistics as well as the number (%) of patients who have:

- 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 SC injections (for the entire LTS study)

5.1.6.2. Exposure to Investigational Product

The treatment exposure to fasinumab and placebo SC doses will be calculated as:

- (Date of last study drug dose – date of first study dose) + 28

The duration of exposure in will be summarized for each treatment group using the number of patients (n), mean, standard deviation, median, Q1, Q3, minimum, and maximum.

The number (%) of patients with exposure duration periods will be presented by specific time periods. The time periods of interest are specified as: ≥ 1 day, ≥ 29 days, ≥ 57 days, ≥ 85 days, ≥ 113 days, ≥ 141 days, ≥ 169 days, ≥ 197 days, ≥ 225 days, ≥ 253 days, ≥ 281 days, ≥ 309 days, ≥ 337 days

5.1.6.3. Length of Study Observation

The length of the observation period (days) will be calculated as:

- (Date of last study visit [up to End of Follow-up Clinic Visit] – date of first study drug dose) +1.

The length of the total study observation period (days) will be calculated as:

- (Date of last study visit [up to End of Study Phone call] – date of first study drug dose) +1.

The observation duration will be summarized for each treatment group using the number of patients (n), mean, standard deviation, median, Q1, Q3, minimum, and maximum.

The number (%) of patients with observation periods will be presented by specific time periods. The time periods of interest are specified as: ≥ 1 day, ≥ 29 days, ≥ 57 days, ≥ 85 days, ≥ 113 days, ≥ 141 days, ≥ 169 days, ≥ 197 days, ≥ 225 days, ≥ 253 days, ≥ 281 days, ≥ 309 days, ≥ 337 days, ≥ 365 days, ≥ 393 days, ≥ 421 days, ≥ 505 days, ≥ 701 days

5.1.6.4. Protocol Deviations

All major and minor protocol deviations have been collected and reviewed on an ongoing basis throughout the study as described in the Protocol Deviation Definitions Document (PDDD).

Protocol deviations will be summarized for patients incurring any major deviation by count and percentage, and patients incurring each type of major deviation by count and percentage for FAS-LTS.

A patient listing of all major and minor protocol deviations will be provided.

5.1.7. Analysis of Safety Data

The analysis of safety and tolerability will be performed on the SAF-LTS, as defined in Section 3.2.

The safety analysis will be based on the reported AEs and other safety information (clinical laboratory evaluations, vital signs, 12-lead ECG, Physical Examination, etc.).

Treatment-Emergent Potential Clinically Significant Values (PCSV) in laboratory variables, vital signs and ECG are defined in Appendix 11.2.

Period of observation: The observation period will be divided into three segments: pre-treatment, on-treatment and post-treatment.

- The pre-treatment period is defined as the time between when the patients give informed consent and the start of study drug.
- The LTS on-treatment period is defined as the time from first dose of study drug up to 28 days after the last dose of study drug. The LTS post-treatment period is defined as the time starting 29 days after last dose of study drug (after the on-treatment period) to up to 24 weeks post the last dose of study drug (up to week 72).

Day 1 is the first day of study drug, Day –1 is the day before Day 1, and there is no Day 0.

The time interval to detect any on-treatment event or abnormality is between the first dose of double-blind study drug injection and the end of treatment plus 28 days. Data collected outside this interval will be excluded from the estimation of descriptive statistics and identification of abnormalities for laboratory evaluations, ECGs and vital signs. All post-baseline data during the interval will be using in the PCSV analysis including scheduled and unscheduled assessments.

5.1.7.1. Primary Safety Endpoints

Incidence rate ratio estimates and 2-sided 95% confidence interval will be computed using Generalized Estimating Equations with a log-linked Poisson model via the PROC GENMOD procedure if there are events in the placebo group. The model will specify the use of a Poisson probability distribution with an offset= log (patient-observation period days) and model terms for treatment-as-received and each randomization strata. The 95% confidence interval for the

estimates of the difference in incidence rates will be computed using the same model. If there is no event in the placebo group, incidence rate ratio will not be calculated and confidence intervals for the incidence rate difference will be computed using Wald method. The incidence rate estimates for each arm, the estimates of the incidence rate ratio and incidence rate difference between fasinumab and placebo will be provided with the corresponding 95% confidence interval.

AE and SAE incidence will be summarized by treatment group based on the SAF-LTS by treatment group and combined fasinumab group.

Continuous variables will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics based on the SAF-LTS by treatment group and combined fasinumab group.

5.1.8. Exploratory Safety Endpoints

Other safety endpoints in the study are:

- The proportion of patients taking rescue medication, number of days on rescue medication, and weekly average usage of rescue medication
- The percent of patients using standard-of-care analgesic medication from week 16 to week 52
- Time to JR decision
- Survey of Autonomic Symptoms Scores:
  - number of patients reporting health symptoms for each symptom/health problem assessed at each scheduled visit
  - number of symptoms reported and total symptom impact score at each scheduled visit
- Time to AA, time to DA

The exploratory safety variables comparing incidence rate of each fasinumab dose group and placebo will be analyzed using the same method as the primary safety endpoints.

The exploratory safety variables comparing change from baseline scores of each fasinumab dose group and placebo will be analyzed using the same method as the primary safety endpoints.

Time to event endpoints will be analyzed using Kaplan-Meier approach and Cox regression will be used for comparing each fasinumab dose group and placebo by obtaining hazard ratios and their confidence intervals. The Cox regression model will include the fixed categorical effects of treatment-as-received and randomization strata.

Additionally, sensitivity analysis of the primary endpoint of incidence of destructive arthropathy as well as incidence of DA and JRs will be analyzed excluding patients who used NSAID during the trial.

Rescue Medication

The percentage of patients who use rescue medication between baseline and week 16 will be summarized by the treatment group for FAS-LTS.

Number of days patients used rescue medication during the treatment period (Day1 to Week 2, Week 2 to Week 4, Week 4 to Week 8, Week 8 to Week 12, Week 12 to Week 16...) will be summarized descriptively by treatment group. Weekly average amount of rescue medication use will be summarized by treatment group.

5.1.8.1. Adverse Events

The verbatim text, the preferred term, and the primary SOC will be listed in patient listings. Summaries that include frequencies and proportions of patients reporting AEs will include the preferred terms and the SOCs.

- *Pre-Treatment Adverse Events* are defined as AEs that developed or worsened during the pre-treatment period.
- *Treatment-Emergent Adverse Events (TEAE)* are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the on-treatment period.
- *Post-Treatment Adverse Events* are defined as AEs that developed or worsened more than 28 days after the last dose of study drug.

The focus of adverse event reporting in the clinical study report will be on TEAEs. Post-treatment AEs and AEs during the study will be summarized similarly as TEAEs.

Summaries of TEAEs by treatment group will include:

- Overview of TEAEs, summarizing number of events, summarizing number and percentage of patients within the specified category
  - Total number of TEAEs
  - Total number of Serious TEAEs
  - Patients with any TEAEs
  - Patients with any Serious TEAEs
  - Patients with any TEAEs leading to death

  - Patients with any TEAEs leading to withdrawal from study
  - Patients with any TEAEs leading to permanent study treatment discontinuation
- All TEAEs by SOC and PT
- All TEAEs by SOC, PT, severity
- Study drug related TEAEs by SOC and PT
- TEAEs resulting in Permanent Study Drug Discontinuation by SOC and PT
- AESI by SOC and PT
- Serious TEAEs by SOC and PT
- Non-serious TEAEs by SOC and PT

Listing to include:

- Listing of AEs leading to death
- Listing of TEAEs leading to permanent study treatment discontinuation
- Listing of TEAEs leading to withdrawal from study
- Listing of Patients with Serious TEAEs
- Listing of Patients with AESIs
- Listing of all Joint Replacements

Counts will be provided according to treatment group and combined fasinumab group for each PT within each primary SOC. Percentages will be calculated based on the SAF-LTS in each treatment group.

Primary SOCs will be sorted by decreasing frequency in the combined fasinumab group. Within each primary SOC, PTs will be sorted by decreasing frequency in the combined fasinumab group. For tables presenting severity of events, the worst severity will be chosen for patients with multiple instances of the same event.

A second type of table with counts of each primary SOC in decreasing order of frequency will be provided. A third type of table with counts of each PT in decreasing order of frequency will also be provided. TEAEs with preferred terms ≥5% in any treatment group will be summarized in the report.

5.1.8.2. Adverse Events of Special Interest

AESIs will be listed and summarized by treatment group based on the SAF-LTS. Differences in event rate for AESIs between fasinumab and placebo will be estimated using exact binomial confidence intervals.

Radiograph data related to AA including change from baseline in joint space width will be summarized by SAF over time. Within index type, Knee Society Score questionnaire or Harris Hip Score questionnaire results will be listed.

5.1.8.3. Clinical Laboratory Measurements

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics based on the SAF-LTS by treatment group and combined fasinumab group.

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

Listings will be provided with flags indicating the out of laboratory range values.

A Treatment-Emergent Potential Clinically Significant abnormal value (PCSV) is a laboratory value that was normal at Screening and Baseline but became abnormal and met PCSV criteria after treatment with study drug. Definition of PCSV is listed in Appendix 11.2. Treatment Emergent Potentially clinically significant values (PCSVs) will be summarized based on the SAF-LTS by treatment group and combined fasinumab group. Additional exploratory analyses using alternative cut-points may be conducted.

For hs-CRP, plots of means and medians of the observed values and change from baseline over time will presented by treatment group.

For hs-CRP, subgroup analysis will be performed for the following:

- Baseline hs-CRP ([0 – 3], [>3 -10], [>10])
- Adjudicated Arthropathy category 1 (patients without / with AA)
- Adjudicated Arthropathy category 2 (patients without AA, patients with RPOA-1, and patients with non-RPOA-1 AA)
- Destructive Arthropathy category (patients without AA, patients with non-DA AA, patients with DA)

5.1.8.4. Analysis of Vital Signs

Vital signs (temperature, pulse, blood pressure, orthostatic blood pressure/heart rate, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics by treatment group and combined fasinumab for the SAF-LTS.

PCSV summary including orthostatic hypotension will be constructed for on-treatment period, post-treatment period and overall during the LTS study.

5.1.8.5. Analysis of 12-Lead ECG

ECG parameters (Ventricular Rate, PR Interval, QRS Interval, QT Interval, RR Interval, QTcF QTcB interval) will be summarized by baseline and change from baseline to each scheduled and collected assessment time. PCSV summary of ECG parameters will be provided for on-treatment period (for LTS study), post-treatment period, and overall for the SAF-LTS.

ECG status (i.e. normal, abnormal) will be reported. Shift tables will be provided to present the post-baseline status according to the baseline status (normal or missing / abnormal) by treatment.

5.1.8.6. Physical Exams

The number and percentage of patients with new-onset abnormal physical examinations will be summarized by body system by visit based on the SAF-LTS.

5.1.8.7. Joint Pain Questionnaire

The number and percentage of patients with significantly worse joint pain will be summarized by visit and joint based on the SAF-LTS.

5.1.8.8. Arthropathy Adjudications

The number and percentage of patients with images requiring arthropathy adjudication as well as the number and percentage of those patients with confirmed adjudicated arthropathy will be summarized by based on the SAF-LTS. Subtypes of AAs and outcomes of AAs will also be summarized. Patient listings of cases confirmed by adjudication will be provided.

5.1.8.9. Neurological Exam

The number and percentage of patients with new-onset abnormal neurological examinations will be summarized by Neurological evaluations by visit based on the LTS-SAF.

5.1.8.10. Analysis of Pharmacokinetics and Drug Concentration Data

Summaries of concentrations of functional fasinumab will be presented by nominal time point and dose. Plots of mean or median concentration of functional fasinumab will be presented by nominal day and dose.

5.1.9. Analysis of Anti-Drug Antibody Data

The ADA variables described in Section 4.7 will be summarized using descriptive statistics by dose/cohort group in the ADA analysis set. Prevalence of treatment-emergent and treatment-boosted ADA will be assessed as absolute occurrence (N) and percent of patients (%), grouped by study cohorts. For treatment emergent ADA, occurrence (N) and percent of patients (%) with persistent, transient and indeterminate ADA will be reported. The influence of treatment-emergent or treatment-boosted ADA assay response on individual PK profiles may be evaluated.

Listings of ADA positivity and titers presented by patient, time point, and dose cohort/group will also be provided.

Correlation analysis of safety versus treatment-emergent ADA positivity status may be performed on the SAF. Assessment will focus on the following safety events:

- Hypersensitivity (SMQ: Hypersensitivity [Narrow])
- Anaphylaxis (SMQ: Anaphylaxis[Narrow])

Number (%) of patients with the above-mentioned safety events may be summarized by treatment-emergent ADA positivity status, during the TEAE period.

In addition, correlation analysis of key efficacy endpoints versus treatment-emergent ADA status in patients who discontinued due to lack of efficacy may be summarized.

5.2. Statistical Methods for Efficacy Sub-Study

5.2.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be descriptively summarized by treatment group, combined fasinumab, and overall based on the FAS-substudy. Parameters to be summarized include those described in Section 4.1.

5.2.2. Medical History

Medical history will be descriptively summarized by treatment group, combined fasinumab, and overall based on the FAS-substudy.

5.2.3. Prior / Concomitant Medications

Prior Medications

All prior medications, dictionary coded by WHO, will be descriptively summarized by treatment group, and combined fasinumab based on the FAS-substudy similar to the summary for FAS-LTS.

Concomitant Medications

All concomitant medications, dictionary coded by WHO, will be descriptively summarized by treatment group, and combined fasinumab based on the SAF-substudy similar to the summary for FAS-LTS.

5.2.4. Prohibited Medications

Number and percentage of patients with prohibited medications will be descriptively summarized by treatment group, and combined fasinumab based on the SAF-substudy.

The number of patients with NSAID use during treatment period 1 will be summarized by treatment group, and combined fasinumab.

5.2.5. Patient Disposition

The disposition of patients in the sub-study will be summarized by treatment group, combined fasinumab, and overall for FAS-Substudy.

- Unless otherwise noted, percentages will be calculated using the number of patients randomized in FAS-substudy as the denominator. This will be summarized by treatment group, combined fasinumab, and overall for the efficacy sub-study. Kaplan-Meier plot of time to treatment discontinuation will be provided. Summaries will provide the frequency (and percentage as applicable) of patients that met the criteria for the following variables:

- Patients randomized (defined as having received a randomization number). This row will reflect grouping based on randomization assignment.

- Patients randomized but not treated. This row will reflect grouping based on randomization assignment.

- Patients randomized and treated.

- Patients who completed treatment period 1. Reason for treatment discontinuation during the efficacy sub study and efficacy sub-study withdrawal will be provided.

5.2.5.1. Analysis Set

Summary of the number (and percentage) of patients in each analysis set will be by treatment group, combined fasinumab, and overall for the efficacy sub-study.

Additionally, the following listings will be provided (if applicable):

- Listing of Patients Treated but not Randomized.

- Listing of Patients Randomized but not Treated.

- Listing of Patients Randomized but not Treated with the Randomized treatment.
- Listing of Patient Disposition for all Randomized Patients.
- Listing of Screening Failures and reasons for all screen failed patients.

5.2.6. Extent of Study Treatment Exposure and Compliance

The analysis population for the efficacy sub-study is based on the SAF-substudy.

5.2.6.1. Measurement of Treatment Compliance

Compliance with protocol-defined investigational product will be calculated by treatment group and combined fasinumab as follows:

(Number of actual injections of study drug during the efficacy sub-study exposure period) / (Number of planned injections of study drug during the efficacy sub-study exposure period on or before the time that the patient discontinues from the efficacy sub-study) x 100%

Treatment compliance will be presented by descriptive statistics as well as the number (%) of patients who have:

- 1, 2, 3, and 4 SC injections (for the efficacy sub-study)

5.2.6.2. Exposure to Investigational Product

The treatment exposure to fasinumab and placebo SC doses will be calculated as:

- (Date of last efficacy sub-study drug dose – date of first study drug dose) + 28

The duration of exposure in will be summarized for each treatment group using the number of patients (n), mean, standard deviation, median, Q1, Q3, minimum, and maximum.

The number (%) of patients with exposure duration periods will be presented by specific time periods. The time periods of interest are specified as: $\geq$ 1 day, $\geq$ 29 days, $\geq$ 57 days, and $\geq$ 85 days

5.2.6.3. Length of sub study Observation

The length of the sub study observation (days) will be calculated as: (Date of last efficacy sub-study visit [up to week 16] – date of first study drug dose) +1

The observation duration will be summarized for each treatment group using the number of patients (n), mean, standard deviation, median, Q1, Q3, minimum, and maximum.

The number (%) of patients with observation periods will be presented by specific time periods. The time periods of interest are specified as: $\geq$ 1 day, $\geq$ 29 days, $\geq$ 57 days, $\geq$85 days, and $\geq$ 113 days

5.2.6.4. Protocol Deviations

Protocol deviations will be summarized for patients incurring any major deviation by count and percentage, and patients incurring each type of major deviation by count and percentage for FAS-Substudy. Protocol deviations leading to exclusion from the PPS for the efficacy sub-study (see Section 3.3 for definition) will be summarized for any patients incurring any such deviation by count and percentage, and patients incurring each type of deviation by count and percentage.

5.2.7. Analysis of Efficacy Data

5.2.7.1. Analysis of Primary Efficacy Variable(s)

5.2.7.1.1. Primary Efficacy Analysis

The co-primary efficacy endpoints in the efficacy sub-study are:

- Change from baseline to week 16 in the WOMAC pain subscale score
- Change from baseline to week 16 in the WOMAC physical function subscale score

The primary treatment comparison for the WOMAC pain subscale score as well as the WOMAC physical function subscale score is declared superior only if the comparisons are significant for both WOMAC pain and physical function subscale scores at any of the allowed doses. Hence there are 6 hypotheses to be tested between the primary and key secondary endpoints. A hierarchical procedure will be used to control the overall Type-1 error rate at 0.05 for the 2 co-primary endpoints and the secondary endpoints across the 2 dose regimens. Each hypothesis will be formally tested only if the preceding one is significant at the 2-sided 0.05 significance level. The hierarchical testing order for the 6 hypothesis is as follows:

- H_{11}: There is no treatment difference between fasinumab 1 mg Q4W and placebo in WOMAC pain or physical function subscale scores at week 16 versus there is a treatment difference in WOMAC pain and physical function subscale scores at week 16
- H_{12}: There is no treatment difference between fasinumab 1 mg Q4W and placebo in Patient Global Assessment score at week 16 versus there is a treatment difference in Patient Global Assessment score at week 16
- H_{13}: There is no treatment difference between fasinumab 1 mg Q4W and placebo in the proportion of patients with ≥30% improvement in the WOMAC pain subscale scores at week 16 versus there is a treatment difference in proportion of patients with ≥30% improvement in WOMAC pain at week 16
- H_{21}: There is no treatment difference between fasinumab 1 mg Q8W and placebo in WOMAC pain or physical function subscale scores at week 16 versus there is a treatment difference in WOMAC pain and physical function subscale scores at week 16

- H_{22}: There is no treatment difference between fasinumab 1 mg Q8W and placebo in Patient Global Assessment score at week 16 versus there is a treatment difference in Patient Global Assessment score at week 16

- H_{23}: There is no treatment difference between fasinumab 1 mg Q8W and placebo in the proportion of patients with ≥30% improvement in the WOMAC pain subscale scores at week 16 versus there is a treatment difference in proportion of patients with ≥30% improvement in WOMAC pain at week 16

The estimand for the primary efficacy objective is the difference in means between each fasinumab dose+protocol-defined rescue medication and placebo+protocol-defined rescue medication in the change from baseline to week 16 in the WOMAC pain and physical function scores in the FAS-substudy, regardless of whether or not prohibited medication had been taken. Data collected after discontinuing treatment up to week 16 will not be used in the primary efficacy analysis but used in a treatment policy sensitivity analysis. The missing data for patients who discontinued treatment due to lack of efficacy or AEs will be imputed with values centered at the mean baseline value of the treatment group that patients were randomized to. The missing data for patients discontinued treatment due to other reasons will be imputed under missing-at-random assumption using the regression method with adjustment for covariates including treatment group, randomization strata, and baseline score. Intermittently missing data will be imputed using Markov Chain Monte Carlo method.

The primary efficacy variables will be analyzed using a multiple imputation approach with mixed-effect model for repeated measure (MMRM) based on the FAS-substudy with adjustment for missing data due to treatment discontinuation for the reasons of lack of efficacy or AEs assuming the WOMAC scores would on average return to baseline values. Missing data up to week 16 will be imputed 50 times to generate 50 complete data sets by using the SAS procedure PROC MI following the 3 steps below:

- Step 1: The monotone missing pattern is induced by Markov Chain Monte Carlo (MCMC) method in MI procedure using seed number [redacted]

- Step 2: The missing data at subsequent visits will be imputed using the regression method for the monotone pattern with seed number [redacted] and adjustment for covariates including treatment groups, randomization strata, relevant baseline and all values at preceding visits.

- Step 3: The initially missing and now imputed data for patients discontinued from the study treatment due to lack of efficacy or AEs will be adjusted to be centered at the mean baseline value for that treatment group, i.e., final imputed score = imputed score under MAR - (mean change from baseline score at the post-baseline time point for the treatment group based on patients on treatment with non-missing data at that time point).

Each imputed data set will be analyzed using the MMRM with terms for baseline score corresponding to the primary efficacy variable (e.g. WOMAC pain subscale score at baseline for the analysis of change from baseline in WOMAC pain subscale score), treatment, randomization strata, visit, and treatment by visit interaction. The MMRM will be performed using the MIXED procedure in the Statistical Analysis System (SAS) with an unstructured covariance matrix to model the within-patient errors. Denominator degrees of freedom will be estimated using Kenward-Roger's approximation.

- The results from the 50 analyses will be combined using Rubin's formulae (PROC MIANALYZE). The least squares mean estimates for the mean change from baseline to week 16, as well as the difference of the estimates between fasinumab and placebo, with the corresponding standard error, p-value and associated 95% confidence interval will be provided.

5.2.7.1.2. Sensitivity Analyses

Sensitivity analyses will be performed to assess the robustness of the results generated for the primary efficacy variables.

Analysis of Treatment Policy Estimand

Sensitivity analysis of treatment policy estimand for the co-primary endpoints will be performed using similar analysis method as the primary efficacy analysis. The treatment policy estimand is the difference in means between each fasinumab dose+protocol-defined rescue medication and placebo+protocol-defined rescue medication in the change from baseline to week 16 in the WOMAC pain and physical function scores in the FAS-substudy, regardless of study treatment discontinuation prior to week 16 and regardless of whether or not prohibited medication had been taken. Hence, data from all patients, including data collected after discontinuing treatment up to week 16 will be used in this sensitivity analyses. Missing data for patients discontinued from the study up to week 16 will be imputed assuming the WOMAC scores would on average return to baseline values using the same approach as in Section 5.2.7.1.1.

Tipping Point Analysis

Sensitivity analysis using a tipping point approach with multiple imputation will be performed to assess the robustness of the results due to data that may be missing not-at-random (MNAR).

This approach will introduce a sensitivity parameter, δ, corresponding to a percentage (*e.g., 20%, 40%, ..., 100%, 200%, ...*) of the treatment effect at each corresponding visit. Estimations will be performed using multiple imputation methodology. Missing data up to week 16 time-point will be imputed 50 times to generate 50 complete datasets by using SAS procedure PROC MI for each δ following the 2 steps below:

- Step 1: The monotone missing pattern is induced by Markov Chain Monte Carlo (MCMC) method in MI procedure using seed number [redacted].

- Step 2: The missing data at subsequent visits will be imputed using the regression method for the monotone pattern with seed number [redacted] and adjustment for covariates including treatment groups, randomization strata, relevant baseline and values from preceding visits. For missing data due to adverse events or lack of efficacy, δ will be added to the imputed values (δ = 0 corresponds to the MAR assumption).

Each imputed data set will be analyzed using the MMRM model with treatment, randomization strata, and relevant baseline included in the model. For each δ the SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 50 analyses using Rubin's formula. By progressively increasing δ, the sensitivity analysis will explore the tipping points, e.g., δ value when the p-value for a treatment comparison is above 0.0167, 0.0333 or 0.05. Results will be then summarized using summary tables and graphs.

Per Protocol Set Analysis

Sensitivity analyses based on the PPS will be performed using the MMRM approach.

Subgroup Analysis

Descriptive analyses will be performed on the primary endpoints and key secondary endpoint of PGA to summarize the treatment effects across subpopulations defined by baseline randomization strata (index joint and K-L score category), demographics (age group, sex, race) and baseline characteristics (weight and BMI categories). Subgroup analysis based on other medical conditions may also be performed. Forest plots for the subgroup analysis will be provided.

5.2.7.2. Analysis of Key Secondary Efficacy Variable(s)

Analyses of continuous variables in key secondary endpoints will use the same analysis method as the primary efficacy variables.

Analysis of categorical variables in key secondary endpoints, the Cochran-Mantel-Haenszel approach stratified by the randomization strata will be used with missing data considered as non-response.

Control for multiplicity for both the primary and key secondary efficacy analyses are described in Section 5.2.7.1.

5.2.7.3. Analysis of Additional Secondary Efficacy Variable(s)

Analyses of continuous variables in other secondary endpoints will use the same analysis method as the primary efficacy variables.

No control for multiplicity will be made for these analyses. Tests for comparing each fasinumab dose versus placebo will utilize a nominal 2-sided alpha level of 0.05.

NRS

For the analysis of average weekly walking index joint pain using the NRS pain scale, baseline is defined as the average of the non-missing values during 7 days prior to taking study drug. For each week, the average of the non-missing values during the 7 days on or prior to that week will be used. If all values are missing for the 7 days, the value for that week is set to missing.

The MMRM model will be used for the analysis with terms for the randomization strata (K-L category [2-3 vs. 4] and index joint [hip or knee], geographic region), treatment, week treatment-by-week interaction as fixed effects, and baseline NRS value as a covariate. The least-squares (LS) means for the mean change from baseline to each week as well as the LS mean differences between fasinumab doses and placebo, with their corresponding standard errors (SEs), p-values and associated 95% confidence intervals, will be provided from the MMRM. If the model does not converge using unstructured covariance matrix, ARH(1) covariance structure will be used.

Responder analyses

The percentage of patients who are responders based on WOMAC pain and physical function subscale scores and Patient Global Assessment scale scores defined by at least a 30% reduction and at least a 50% reduction from baseline to each post-baseline week will be summarized and plotted by the treatment group. The percentage of patients who are responders based on the Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative and The Outcome Measure in Rheumatology (OMERACT-OARSI) responder criteria (Appendix 11.3) will be summarized and plotted by the treatment group. Cochran-Mantel-Haenszel (CMH) test, stratified by the randomization strata will be applied for the responder analysis. Missing data is considered as non-response in this analysis.

Cumulative distribution of percent change from baseline in WOMAC pain and physical function subscale scores and Patient Global Assessment scale scores will be presented by treatment group. The cumulative distribution plot displays a continuous plot of the percent change from baseline on the X-axis and the percent of patients experiencing that change on the Y-axis. Different responder definitions can be identified along the cumulative distribution curve.

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

6.1. Definition of Baseline for Variables

Unless otherwise specified, the baseline assessment for all measurements will be the latest available valid measurement prior to randomization.

6.2. Data Handling Conventions for Efficacy Data

Missing data items for questionnaires

WOMAC scores will be computed when one pain item, one stiffness item, or at most 3 physical function items are missing. The missing items will be imputed by the mean of available items within the same subscale. The scores will be set to missing if more items are missing.

6.3. General Data Handling Conventions

Date of last dose of study treatment

The date of the last injection is equal to the last date of administration reported on injection administration case report form page, or missing if the last administration date is unknown.

Handling of Adverse Event and Injection Site Reaction Severity

If the severity of a TEAE is missing, it will be classified as “severe” in the frequency tables by severity of TEAEs.

Handling of Adverse Event Relatedness

If the assessment of relationship of a TEAE to the study drug or study conduct is missing, it will be classified as “related”.

Handling of Adverse Events or Concomitant Medications with missing or partial start date/time

If the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the intake of study medication, except if an incomplete date (eg, month and year) clearly indicates that the event started prior to treatment. Thus, if the AE does not clearly indicate that the AE started prior to treatment or after the TEAE period, the AE will

be classified as "treatment-emergent". This is for classification purposes in the frequency tables and will not be used in the listings.

Handling of Adverse Events or Concomitant Medications with missing or partial end date/time

When only year is present, missing AE/concomitant medication end day and month will be imputed to the earlier of (study end date, 31DECYYYY).

When both month and year are present, missing AE/concomitant medication end date will be imputed to the last day of the month.

There will be no attempt to impute completely missing AE/concomitant medication end dates. Events with an end date missing will be assumed to be ongoing at the time of data cut off.

Handling of Adverse Events classification with missing or partial date/time of first study drug administration

When the date and time of first study drug dose is missing, the date of randomization will be used as the start date for classification of AEs.

When the time of the first study treatment dose is missing, all AEs that occurred on the date of the first study drug dose will be considered as TEAEs.

Missing/Incomplete Medical history dates

Medical history start dates are used to determine the duration of OA at baseline per eCRF data. Completing missing medical history dates will not imputed. Missing month will be imputed to January and missing day will be imputed to the first day of the month.

Laboratory Safety Variables below LLOQ or above ULOQ

For central laboratory data below the lower limit of quantification (LLOQ), half of the lower limit value (i.e., LLOQ/2) will be used for quantitative analyses.

Missing laboratory, ECG, vital sign, physical exam, neurological exam

No imputations for missing laboratory data, ECG data, vital sign data, physical examination, or neurological examination data will be made.

Handling of Potentially Clinically Significant Abnormalities

If a patient has a missing baseline value they will be grouped in the category "normal/missing at baseline".

For PCSAs with 2 conditions, one based on a change from baseline value and the other on a threshold value or a normal range, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; eg, for eosinophils the PCSA is >0.5 GIGA/L or >ULN if ULN ≥0.5 GIGA/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

6.4. Visit Windows

By-visit analysis (including efficacy, laboratory data, vital signs, ECG, ADA) will be summarized by the nominal visit number. Assessments taken outside of protocol allowable windows will be displayed according to the case report form (CRF) assessment recorded by the investigator. For assessments without a nominal visit number such as Unscheduled, EOT, and EOS assessments, a visit number will be assigned based on the actual visit date using the study day analysis window based on the targeted visit study day in Appendix 11.1 Table 2 Schedule of Events.

The following visit windows will be used to map the unscheduled visits, early end of treatment visits, early study termination visits and daily electronic dairy entries, based on the study day:

Visit No.	Visit	Targeted Study Days*	Analysis Window in Study Days
1	Screening	Day -30 to Day -11	≥ -30 and ≤ -11
2	Pre-randomization Phone Call	Day -10 to -7	-10 to -1
3	Baseline	1	≤ 1
	Week 1 (efficacy sub-study)	8	[2, 11]
	Week 2 (efficacy sub-study)	15	[12, 22]
4	Week 4	29	[23,43](efficacy substudy);[2,43] (LTS)
5	Week 8	57	[44,71]
6	Week 12	85	[72,99]
7	Week 16	113	[100,127]
8	Week 20	141	[128,155]
9	Week 24	169	[156,183]
10	Week 28	197	[184,211]
11	Week 32	225	[212,239]
12	Week 36	253	[240,267]
13	Week 40	281	[268,295]
14	Week 44	309	[296,323]
15	Week 48	337	[324,351]
16	Week 52	365	[352,393]
17	Week 60	421	[394,463]
18	Week 72	505	≥464

*Study days are calculated from the first dose of study drug (Day 1).

If multiple measurements occur within the same visit window, the following rules will be used to determine the analysis value:

- When multiple valid measurements occur within the same visit window, the one closest to the target study day will be used in the analysis.
- When multiple valid measurements occur within equal distance from the target study day, the value after the target study day will be used in the analysis.

Both scheduled and unscheduled measurements will be considered for determining abnormal/PCSV values from laboratory, vital sign or ECG as well as the baseline values.

6.5. Unscheduled Assessments

The determination of baselines and values at the end of treatment for both efficacy and safety variables will be based on available assessments of scheduled and unscheduled visits. For by visit summaries, unscheduled visit will be mapped to a visit using the visit windows described in Section 6.4 and then included in the by-visit summaries.

7. TIMING OF STATISTICAL ANALYSES

The efficacy sub-study and LTS study analyses will be performed based on three different database locks:

- **1st Step Analysis:** takes place when the last efficacy sub-study patient completes the efficacy sub-study visits and includes all patient data collected up to the week 16 visit. The primary efficacy analysis for the sub-study will be conducted at this time. No alpha adjustment is needed, as the week 16 efficacy sub-study analysis will be the final primary efficacy analysis. Safety analysis will be performed for internal safety monitoring. Patient level results will not be disclosed to any site-facing personnel or to any personnel directly involved with the conduct of the study.

- **Week 72 analysis:** takes place when the patient data collected up to the time the last LTS patient completes the LTS study visits and assessments at week 72 visit. The week 72 primary safety analysis will be conducted at this time.

- **Final analysis**: takes place when patient data collected up to the time the last LTS patient completes assessments at week 100. The only additional analysis to be conducted at this time is the analysis of incidence of JRs at the telephone survey approximately 52 weeks after the last dose of study drug and updating of outputs with any data change from the week 72 database lock.

Individuals involved in the 1st step analysis of the study will not be involved in the conduct of the study after the 1st step database lock until after the week 72 database lock. The first step analysis process, the measures used to protect the blind and the integrity of the study, the communication plan, and the confidentiality agreement will be described in a separate document. The results of the first analysis will not be used to change the conduct of the ongoing study in any aspect.

8. INTERIM ANALYSES

No interim efficacy analysis is planned. Additional interim analysis of safety data may be performed for regulatory or internal decision-making purposes.

9. SOFTWARE

All clinical data analyses will be done using SAS Version 9.4 and above.

10. REFERENCES

Bretz, F., W. Maurer, W. Brannath, and M. Posch. A graphical approach to sequentially rejective multiple test procedures. Stat Med. 2009. 28:586-604.

11. APPENDIX

11.1. Schedule of Events and Visits

Study assessments and procedures are presented for all patients for screening through week 16 in Table 1 and for week 20 through week 52 in Table 2. Study assessments and procedures only for patients participating in the efficacy sub-study are shown in Table 3. Study assessments and procedures are presented in Table 4 for the Follow-up Period (52 weeks after the last treatment) and Table 5 shows follow-up assessments for patients who undergo JR surgery during the study.

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Table 1: Schedule of Events - Screening through Week 16 Visit

	Screening Period	Pre-Randomization Period	Treatment Period				
		Pre-Randomization Phone Call					
Study Week			(Baseline)	4	8	12	16
Study Day (visit window)	up to 30 days	7 to 10 days	1	29 (±7)	57 (±7)	85 (±7)	113 (±7)
Screening/Baseline:							
Informed Consent	X						
Inclusion/Exclusion[1]	X	X	X				
Genomics sub-study informed consent[2]	X						
Medical History	X						
Medication history	X						
Demographics	X						
Height	X						
Electrocardiogram	X						
Bilateral radiograph (knee, hip, shoulder)[3]	X[14]						
WOMAC Pain Subscale	X[4]		X				
MRI[3]	X						
Randomization			X				
Treatment:							
Discontinue non-study pain meds		X					
SC Study Drug Injection[5]			X	X	X	X	X
Dispense paracetamol/acetaminophen			X	X	X	X	X

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Study Week	Screening Period	Pre-Randomization Period	Treatment Period				
		Pre-Randomization Phone Call					
			(Baseline)	4	8	12	16
Study Day (visit window)	**up to 30 days**	**7 to 10 days**	**1**	**29 (±7)**	**57 (±7)**	**85 (±7)**	**113 (±7)**
Paracetamol/acetaminophen accountability				X	X	X	X
Dispense NSAID medication							X
Recording of rescue treatment use in diary[6]			X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X
Safety:							
Weight	X						X
Vital Signs[7]	X		X	X	X	X	X
Physical Examination	X						X
Injection site evaluation			X	X	X	X	X
Orthostatic blood pressure[7]	X		X	X	X	X	X
Joint Pain Questionnaire	X		X	X	X	X	X
Survey of autonomic symptoms	X		X	X	X	X	X
Neurologic examination	**Full**		**Brief**	**Brief**	**Brief**	**Brief**	**Full**
Adverse Events	X	X	X	X	X	X	X
Event-triggered imaging[8]				X	X	X	X
Pre-op questionnaire (JR)[9]							
Laboratory Testing:							
Hematology	X						X
Blood Chemistry	X			X	X		X
Erythrocyte sedimentation rate	X						

Study Week	Screening Period	Pre-Randomization Period	Treatment Period				
		Pre-Randomization Phone Call					
			(Baseline)	4	8	12	16
Study Day (visit window)	**up to 30 days**	**7 to 10 days**	**1**	**29 (±7)**	**57 (±7)**	**85 (±7)**	**113 (±7)**
HbA1c	X						
FSH and estradiol[10]	X						
Pregnancy test (WOCBP)	Serum[11]		Urine[12]	Urine[12]	Urine[12]	Urine[12]	Urine[12]
Urinalysis and Urine Creatinine and Phosphorous	X			X	X		X
PK/Drug Concentration and ADA Samples:							
PK/Drug concentration sample[13]							X
ADA sample[13]			X				X
Genomics sub-study sample[2]			X				
Research serum/plasma sample[13]			X	X	X		X

ADA: Anti-drug antibody; FSH: Follicle stimulating hormone; JR: Joint replacement; MRI: Magnetic resonance imaging; NSAID: Non-steroidal anti-inflammatory drug; PK: Pharmacokinetic; WOCBP: Women of child-bearing potential; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

1. HIV and/or hepatitis testing will be performed on a country-by-country basis, according to local guidelines if required by regulatory authorities or ethics boards
2. Only for patients who provide written informed consent for the optional genomics sub-study. The sample should be collected at the baseline visit, but may be collected at any subsequent visit during the study.
3. After the patient has otherwise met study eligibility criteria assessed during the screening period, an MRI must be performed before the pre-randomization phone call for the index and contralateral joint as well as any knee or hip joint that has a baseline K-L score ≥3. Confirmation from the central reader that there are no exclusionary findings on the MRI must be received before the patient can be randomized.
4. At the screening visit, the WOMAC pain sub-scale will be evaluated for both knees and both hip joints.
5. Study drug administration will be the last procedure at each dosing visit, and will be done after all laboratory samples have been collected and all study assessments and procedures are performed. Patients should be observed in the clinic for approximately 1 hour after administration of study drug for evidence of a hypersensitivity reaction.

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6. Patients will be provided with a diary for recording their daily use of paracetamol/acetaminophen beginning on day 1 through the week 52 visit and their NSAID use from week 16 through week 52.
7. If the pulse is less than 45 bpm at any visit after the randomization visit, an ECG with rhythm strip will be obtained and sent to the central reader to confirm the heart rate and rhythm.

Imaging (X-ray and/or MRI) will be considered for worsening joint pain despite treatment with analgesics, which in the opinion of the investigator, is inconsistent with the normal progression of OA and lasts for at least 2 weeks (or less, at the discretion of the investigator). Additionally, pre-operative imaging for any JR should be submitted for adjudication, if possible.

8. In the event that a patient must undergo JR surgery during the treatment or follow-up periods, he or she will be discontinued from study drug and asked to return for a pre-operative visit, and for follow-up safety evaluations 4 weeks and 20 weeks after surgery (Table 5). The pre-operative visit should be completed before JR surgery if at all possible. Joint replacement questionnaires are Knee Society Score questionnaire for knee replacements or Harris Hip Score questionnaire for hip replacements.
9. To be performed only if postmenopausal status has to be assessed for female patients ≤59 years of age.
10. In the event of a positive serum pregnancy test result, the patient should be withdrawn from study drug and should be asked to return to the clinic for all remaining study visits per the visit schedule (see Section 5.3.2).
11. In the event of a positive urine pregnancy test result, the patient should have a serum pregnancy test with a negative result in order to continue study participation. If the serum pregnancy test is positive, the patient should be withdrawn from study drug and should be asked to return to the clinic for all remaining study visits per the visit schedule (see Section 5.3.2).
12. PK, ADA, and research samples may also be drawn at any scheduled visit or unscheduled visit if a patient experiences a treatment-related safety TEAE.
13. Historical radiographs may be acceptable as outlined in the study imaging acquisition guidelines.

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Table 2: Schedule of Events – Week 20 Visit through Week 52 Visit

Study Week	Week 20 Clinic Visit	Week 24 Clinic Visit	Week 28 Clinic Visit	Week 32 Clinic Visit	Clinic Visits Between Week 36 and End of Treatment	Week 52 or End of Treatment Visit[1]	Early Termination/JR Pre-operative Visit
Visit Window	**Q4W (±7 days)**	**(±7 days)**	**(±7 days)**	**(±7 days)**	**(±7 days)**	**(±7 days)**	
Treatment:							
SC Study Drug Injection[2]	X	X	X	X	X[9]		
Dispense paracetamol/acetaminophen and NSAID medication	X	X	X	X	X		
Paracetamol/acetaminophen /NSAID accountability	X	X	X	X	X	X	X
Recording of rescue treatment use in diary [3]	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X
Safety:							
Weight						X	X
Vital Signs[4]	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X
Electrocardiogram			X			X	X
Injection site evaluation	X	X	X	X	X		
Orthostatic blood pressure	X	X	X	X	X	X	X
Joint Pain Questionnaire	X	X	X	X	X	X	X
Survey of autonomic symptoms	X	X	X	X	X	X	X
Neurologic examination	**Full**	**Full**	**Full**	**Full**	**Full**	**Full**	**Full**
Bilateral radiograph (knee, hip, shoulder) [10]		X				X	X
Adverse Events	X	X	X	X	X	X	X

Study Week	Week 20 Clinic Visit	Week 24 Clinic Visit	Week 28 Clinic Visit	Week 32 Clinic Visit	Clinic Visits Between Week 36 and End of Treatment	Week 52 or End of Treatment Visit[1]	Early Termination/JR Pre-operative Visit
Visit Window	**Q4W (±7 days)**	**(±7 days)**	**(±7 days)**	**(±7 days)**	**(±7 days)**	**(±7 days)**	
Event-triggered imaging[5]	X	X	X	X	X	X	X
Pre-op questionnaire (JR)[6]							X[5]
Laboratory Testing:							
Hematology				X		X	X
Blood Chemistry				X		X	X
Pregnancy test (WOCBP)	Urine[7]	Urine[7]	Urine[7]	Urine[7]	Urine[7]	Urine[7]	Urine[7]
Urinalysis and Urine Creatinine and Phosphorus				X		X	X
PK/Drug Concentration and ADA Samples:							
PK/Drug conc. sample[8]				X		X	X
ADA sample[8]				X		X	X
Research serum/plasma sample[8]						X	X

ADA: Anti-drug antibody; FSH: Follicle stimulating hormone; JR: Joint replacement; MRI: Magnetic resonance imaging; NSAID: Non-steroidal anti-inflammatory drug; PK: Pharmacokinetic; WOCBP: Women of child-bearing potential; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

1. If treatment is stopped for patients (for example, due to conditions in Section 3.1 or Section 5.3.2.1 being met or for other reasons per the patient or investigator), patients should complete the end of treatment/week 52 assessments at their next scheduled visit. All subsequent visits should be conducted according to the schedule of events and all procedures should be completed, except for study medication administration. Imaging does not need to be repeated at a routine visit if all radiographs were conducted within 30 days and submitted for central reading.
2. Study drug administration will be the last procedure at each dosing visit, and will be done after all laboratory samples have been collected and all study assessments and procedures are performed.
3. Patients will record their daily use of paracetamol/acetaminophen and NSAIDs from the week 16 visit through week 52.
4. If the pulse is less than 45 bpm at any visit after the randomization visit, an ECG with rhythm strip will be obtained and sent to the central reader to confirm the heart rate and rhythm.
5. Imaging (X-ray and/or MRI) will be considered for worsening joint pain despite treatment with analgesics, which in the opinion of the investigator, is inconsistent with the normal progression of OA and lasts for at least 2 weeks (or less, at the discretion of the investigator). Additionally, pre-operative imaging for any joint replacement should be submitted for adjudication, if possible.

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6. In the event that a patient must undergo JR surgery during the treatment or follow-up periods, he or she will be discontinued from study drug and asked to return for a pre-operative visit, and for follow-up safety evaluations 4 weeks and 20 weeks after surgery (Table 5). The pre-operative visit should be completed before JR surgery if at all possible. JR questionnaires are Knee Society Score questionnaire for knee replacements or Harris Hip Score questionnaire for hip replacements.
7. In the event of a positive urine pregnancy test result, the patient should have a serum pregnancy test with a negative result in order to continue study participation. If the serum pregnancy test is positive, the patient should be withdrawn from study drug and should be asked to return to the clinic for all remaining study visits per the visit schedule (see Section 5.3.2).
8. PK, ADA, and research samples may also be drawn at any scheduled visit or unscheduled visit if a patient experiences a treatment-related safety TEAE.
9. SC injections will be given Q4W. For patients randomized to 1 mg Q8W, matching placebo will be administered at alternating visits.
10. An MRI may be requested by the imaging vendor after review of the x-rays.

Table 3: Schedule of Additional Events – Only for Patients Participating in the Efficacy Sub-Study (Screening through Week 16 Visit)

	Screening Period	Pre-Randomization Period	Treatment							Early Termination/ JR Pre-Operative Visit
		Pre-Randomization Visit								
Study Week			(Baseline)	1	2	4	8	12	16	Up To Week 16
Study Day (visit window)	up to 30 days	7 to 10 days	1	8 (±1)	15 (±3)	29 (±7)	57 (±7)	85 (±7)	113 (±7)	
Screening:										
Informed consent for sub-study	X									
Efficacy Assessments:										
NRS-average daily walking index joint pain[1]		X	X	X	X	X	X	X	X	X
Patient Global Assessment of OA	X	X	X	X	X	X	X	X	X	X
WOMAC Pain Subscale – index joint only	X[2]		X							
WOMAC Full Survey[3]			X	X	X	X	X	X	X	X
Safety Assessments:										
Orthostatic blood pressure		X	X	X	X	X	X	X	X	X
Urinary drug test	X								X	
PK/Drug Concentration:										
PK/Drug concentration sample			X			X	X		X	X

JR: Joint replacement; NRS: Numerical Rating Scale; OA: Osteoarthritis; PK: Pharmacokinetic; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

1. Walking index joint pain NRS score will be recorded by the site at the pre-randomization visit, and by the patient each day using their diary, starting during the pre-randomization period through week 16.
2. At the screening visit, the WOMAC pain sub-scale will be evaluated for both knees and both hip joints.

3. WOMAC full survey for index joint only

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Table 4: Schedule of Events - Follow-up Period (24 Weeks after Last Treatment) and End of Study Phone Contact (52 Weeks after Last Treatment)

	Phone call 8 weeks post last dose	Clinic Visit 12 weeks post last dose	End of Follow up Clinic Visit 24 weeks post last dose	End of Study Phone call 52 weeks post last dose	Early Termination/JR Pre-Operative Visit
Study Week	**Up to week 56 (±7 days)**	**Up to week 60 (±7 days)**	**Up to week 72 (±7 days)**	**Week 100 (±7 days)**	**During the Follow-up Period**
Treatment:					
Concomitant medications	X	X	X		X
Safety:					
Adverse Events	X	X	X		X
Weight		X	X		X
Vital signs[1]		X	X		X
Physical examination		X	X		X
Electrocardiogram		X	X		X
Orthostatic blood pressure		X	X		X
Joint pain questionnaire		X	X		X
Survey of autonomic symptoms		X	X		X
Neurologic examination		Full	Full		Full
Bilateral radiograph (knee, hip, shoulder)[4]		X	X		X
Event-triggered imaging[2]		X	X		X
Pre-op questionnaire[3]					X
End of study phone contact[5]				X	
MRI of affected joint(s) for AA patients only[6]				X	
Laboratory assessments					
Hematology			X		X

	Phone call 8 weeks post last dose	Clinic Visit 12 weeks post last dose	End of Follow up Clinic Visit 24 weeks post last dose	End of Study Phone call 52 weeks post last dose	Early Termination/JR Pre-Operative Visit
Study Week	**Up to week 56 (±7 days)**	**Up to week 60 (±7 days)**	**Up to week 72 (±7 days)**	**Week 100 (±7 days)**	**During the Follow-up Period**
Blood Chemistry			**X**		**X**
Pregnancy test (WOCBP)			**Urine[8]**		**Urine[8]**
Urinalysis and Urine Creatinine and Phosphorous			**X**		**X**
PK/Drug Concentration and ADA Samples:					
PK/Drug concentration sample[7]		**X**	**X**		**X**
ADA sample[7]			**X**		**X**
Research serum/plasma sample[7]			**X**		**X**

ADA: Anti-drug antibody; JR: Joint replacement; PK: Pharmacokinetic; WOCBP: Women of child-bearing potential.

1. If the pulse is less than 45 bpm, an ECG with rhythm strip will be obtained and sent to the central reader to confirm the heart rate and rhythm.
2. Imaging (X-ray and/or MRI) will be considered for worsening joint pain despite treatment with analgesics, which, in the opinion of the investigator is inconsistent with the normal progression of OA and lasts at least 2 weeks (or less, at the discretion of the investigator). Additionally, pre-operative imaging for any JR should be submitted for adjudication, of possible.
3. In the event that a patient must undergo JR surgery during the treatment or follow-up periods, he or she will be discontinued from study drug and asked to return for a pre-operative visit, and for follow-up safety evaluations 4 weeks and 20 weeks after surgery (Table 5). The pre-operative visit should be completed before JR surgery, if at all possible. Pre-operative images should be submitted to the central reader for adjudication, if available. Joint replacement questionnaires are Knee Society Score questionnaire for knee replacements or Harris Hip Score questionnaire for hip replacements.
4. An MRI may be requested by the imaging vendor after review of the x-rays.
5. The purpose of this phone contact is to ask the patient if they have had or are scheduled (or on a waiting list) to have a JR. Pre-operative images should be submitted to the central reader for adjudication, if available.
6. If the affected joint has undergone JR an X-ray may be substituted for an MRI.
7. PK, ADA, and research samples may also be drawn at any scheduled visit or unscheduled visit if a patient experiences a treatment-related safety TEAE.
8. In the event of a positive urine pregnancy test result, the patient should have a serum pregnancy test.

Table 5: Schedule of Events - Follow-up for Patients Who Undergo Joint Replacement Surgery

	Follow-up Period[1]	
	Post-Operative	**Long-Term**
	Follow-up Visit 1 4 weeks after the date of the joint replacement surgery	**Follow-up Visit 2** 20 weeks after the date of the joint replacement surgery
Follow-up Study Day (Visit Window)	**F/U Day 29 (±5)**	**F/U Day 140 (±7)**
Treatment:		
Concomitant medications	**X**	**X**
Safety:		
Adverse events	**X**	**X**
Vital signs	**X**	**X**
Orthostatic blood pressure[4]	**X**	**X**
Physical examination with joint exam	**X**[1]	**X**
Medical history related to the joint replacement	**X**	**X**
Joint pain questionnaire	**X**	**X**
Post-operative assessment questionnaire[2]	**X**	**X**
Bilateral radiograph (knee, hip, shoulder)[5]	**X**[6]	**X**
Event-triggered imaging[3]	**X**	**X**

F/U: Follow-up

1. All available information for patients who undergo JR surgery must be collected, including placement of the prosthesis, healing of the surgical wound, and the results of the histopathologic examination.
2. Knee Society Score questionnaire for knee replacements or Harris Hip Score questionnaire for hip replacements.
3. Imaging (x-ray and/or MRI) will be performed on any joint following a report of clinically significant worsening or exacerbation of pain in that joint.
4. If it is not possible to obtain orthostatic blood pressure following JR then blood pressure and pulse should be recorded.
5. In the event of more than 1 JR, imaging assessments should be repeated if it has been >60 days since the joints were last imaged. If it has been ≤60 days since imaging assessments were completed, imaging assessments may be completed at the discretion of the investigator. An MRI may be requested by the imaging vendor after review of the x-rays.
6. Imaging will be done at week 4 if not done pre-operatively.

11.2. Reference for Criteria for Treatment-Emergent Potentially Clinically Significant Values (PCSV)

The PCSV criteria below should be used as a reference; the actual criteria for each study should be determined and agreed to by the study team prior to database lock as part of SAP and should be based on the study population, indication, and potential effects of study treatment.

Table 2: Criteria for Treatment-Emergent Potentially Clinically Significant Values (PCSV)

Parameter	Treatment Emergent PCSV	Comments
Clinical Chemistry		
ALT*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. FDA DILI Guidance July 2009. Each category is calculated independently. * At least one level is required; multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, >5 to ≤10, >10 to ≤20, and >20 category for baseline vs. post baseline may be provided

Parameter	Treatment Emergent PCSV	Comments
AST*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. FDA DILI Guidance July 2009. Each category is calculated independently. * At least one level is required; multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and >20 category for baseline vs. post baseline may be provided
Alkaline Phosphatase	>1.5 ULN and baseline ≤ 1.5 ULN	Enzyme activity must be expressed in ULN, not in IU/L. FDA DILI Guidance July 2009.
Total Bilirubin*	>1.5 and ≤ 2 ULN and baseline ≤ 1.5 ULN* >2 ULN and baseline ≤ 2.0 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. FDA DILI Guidance July 2009. * At least one level is required; multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤1.5, >1.5 to ≤2.0 and > 2.0 category for baseline vs. post baseline may be provided
Conjugated Bilirubin	(Direct Bilirubin >35% Total Bilirubin and Total Bilirubin >1.5 ULN) and (Direct Bilirubin <=35% Total Bilirubin or Total Bilirubin <=1.5 ULN) at baseline	Conjugated bilirubin dosed on a case-by-case basis.

Parameter	Treatment Emergent PCSV	Comments
ALT/AST and Total Bilirubin	(ALT >3 ULN and TBILI>2 ULN) and baseline (ALT <=3 ULN **or** TBILI <=2 ULN) (AST >3 ULN and TBILI>2 ULN) and baseline (AST <=3 ULN or TBILI <=2 ULN) (ALT >3 ULN and TBILI>1.5 ULN) and baseline (ALT <=3 ULN or TBILI <=1.5 ULN) (AST >3 ULN and TBILI>1.5 ULN) and baseline (AST <=3 ULN or TBILI <=1.5 ULN)	FDA DILI Guidance July 2009.
ALT/AST and Total Bilirubin and ALP	(ALT >3 ULN and TBILI>2 ULN and ALP < 2 ULN) and baseline (ALT <=3 ULN **or** TBILI <=2 ULN or ALP >=2 ULN) (AST>3 ULN and TBILI>2 ULN and ALP < 2 ULN) and baseline (AST <=3 ULN or TBILI <=2 ULN or ALP >=2 ULN)	FDA DILI Guidance July 2009.
CPK*	>3 and ≤ 10 ULN and baseline ≤ 3ULN* >10 ULN and baseline ≤ 10ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. * At least one level is required; multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤3, >3 to ≤10, and > 10 category for baseline vs. post baseline may be provided

Parameter	Treatment Emergent PCSV	Comments
Creatinine	≥150 µmol/L (Adults) and baseline < 150 µmol/L >=30% change from baseline and <100% change from baseline ≥100% change from baseline	Benichou C., 1994 3 independent criteria
Uric Acid Hyperuricemia Hypouricemia	>408 µmol/L and <=408 µmol/L at baseline <120 µmol/L and >= 120 µmol/L at baseline	Harrison - Principles of internal Medicine 17th Ed., 2008. Two independent criteria
Blood Urea Nitrogen	≥17 mmol/L and <17 mmol/L at baseline	Two independent criteria
Chloride Hypochloremia Hyperchloremia	<80 mmol/L and baseline ≥ 80 mmol/L >115 mmol/L and baseline ≤ 115 mmol/L	Two independent criteria
Sodium Hyponatremia Hypernatremia	≤129 mmol/L and baseline > 129 mmol/L ≥160 mmol/L and baseline <160 mmol/L	Two independent criteria
Potassium Hypokalemia Hyperkalemia	<3 mmol/L and baseline ≥ 3 mmol/L ≥5.5 mmol/L and baseline <5.5 mmol/L	FDA Feb 2005. Two independent criteria
Total Cholesterol	≥7.74 mmol/L and < 7.74 mmol/L at baseline	Threshold for therapeutic intervention.

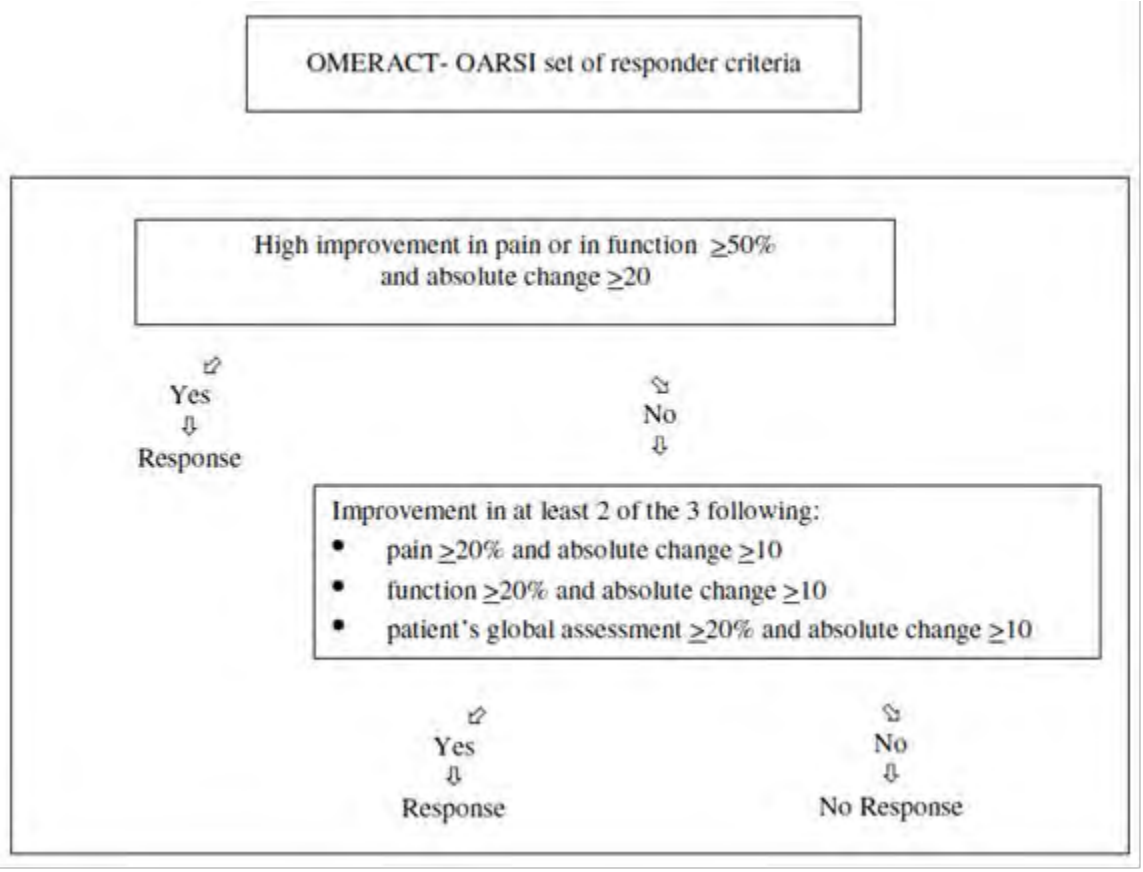
Parameter	Treatment Emergent PCSV	Comments
Triglycerides	≥4.6 mmol/L and < 4.6 mmol/L at baseline	Threshold for therapeutic intervention.
Glucose		
Hypoglycaemia	(≤3.9 mmol/L and <LLN) and (>3.9 mmol/L or >=LLN) at baseline	ADA May 2005.
Hyperglycaemia	≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted) and < 11.1 mmol/L (unfasted); <7 mmol/L (fasted) at baseline	ADA Jan 2008.
HbA1c	>8% and <= 8% at baseline	
Albumin	≤25 g/L and >25 g/L at baseline	
hs-CRP	2 ULN or > 10 mg/L (if ULN not provided)	FDA Sept. 2005
Hematology		
WBC	<3.0 Giga/L and >=3.0 Giga/L at baseline (Non-Black); <2.0 Giga/L and >=2.0 Giga/L at baseline (Black)	Increase in WBC: not relevant.
	≥16.0 Giga/L and < 16 Giga/L at baseline	To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L and <= 4.0 Giga/L at baseline	
Neutrophils	<1.5 Giga/L and >=1.5 Giga/L at baseline (Non-Black);	International Consensus meeting on drug-induced blood cytopenias, 1991.
	<1.0 Giga/L and >=1.0 Giga/L at baseline (Black)	FDA criteria.
Monocytes	>0.7 Giga/L <= 0.7 Giga/L at baseline	
Basophils	>0.1 Giga/L <= 0.1 Giga/L at baseline	

Parameter	Treatment Emergent PCSV	Comments
Eosinophils	(>0.5 Giga/L and >ULN) and (<=0.5 Giga/L or <= ULN at baseline)	Harrison - Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L and > 115 g/L at baseline for male; ≤95 g/L and> 95 g/L at baseline for Female.	Three criteria are independent.
	≥185 g/L and <185 g/L at baseline for Male; ≥165 g/L and < 165 g/L at baseline for Female Decrease from Baseline ≥20 g/L	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v and > 0.37 v/v at baseline for Male; ≤0.32 v/v and > 0.32 v/v at baseline forFemale ≥0.55 v/v and < 0.55 v/v at baseline for Male; ≥0.5 v/v and < 0.5 v/v at baseline for Female	Two Criteria are independent
RBC	Female <3 Tera/L and baseline ≥3 Tera/L ≥6 Tera/L and baseline < 6 Tera/L Male <4 Tera/L and baseline ≥4 Tera/L ≥7 Tera/L and baseline < 7 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L and >=100 Giga/L at baseline ≥700 Giga/L and < 700 Giga/L at baseline	International Consensus meeting on drug-induced blood cytopenias, 1991. Two independent criteria

Parameter	Treatment Emergent PCSV	Comments
Urinalysis		
pH	≤4.6 and > 4.6 at baseline ≥8 and < 8 at baseline	Two independent criteria
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension	Su SBP < 160 mmHg - SBP St – Su ≤ - 20 mmHg DBP St – Su ≤ - 10 mmHg Su SBP ≥ 160 mmHg - SBP St – Su ≤ - 30 mmHg DBP St – Su ≤ - 15 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.

Parameter	Treatment Emergent PCSV	Comments
ECG		Ref.: CPMP 1997 guideline. ICH E14 2005
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
PR	≥220 ms and increase from baseline ≥20 ms	
QRS	≥120 ms & < 120 ms at baseline	
QTc	Absolute values (ms) >450 ms and baseline <=450 ms >480 ms and baseline <=480 ms >500 ms and <= 500 ms at baseline	To be applied to any kind of QT correction formula.
	Increase from baseline Increase from baseline 30-60 ms Increase from baseline >60 ms	ΔQTc>60 ms are the PCSA to be identified in individual subjects/patients listings.

11.3. OMERACT-OARSI set of responder criteria



Note that the criteria in the diagram above are based on standardized score between 0 and 100. For this study, WOMAC pain and physical function score are between 0 and 10, so the absolute change required for response is the required change in the diagram above divided by 10; PGA is 1, 2, 3, 4 or 5, so the absolute change required for response is at least 1 point.

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