STATISTICAL ANALYSIS PLAN
VERSION: FINAL

Clinical Study Protocol Title:	**A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Effects of Fasinumab on Peripheral Nerve Function in Patients with Pain due to Osteoarthritis of the Hip or Knee**
Compound:	**Fasinumab**
Protocol Number:	**R475-OA-1758**
Sponsor:	**Regeneron Pharmaceuticals, Inc.**
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Version/Date:	**Original Statistical Analysis Plan/ 28MAY2020**

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

5-ASA	5-aminosalicylic acid
AA	Adjudicated arthropathy
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
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
ECG	Electrocardiogram
EOS	End of study
EOT	End of treatment
ESR	Erythrocyte sedimentation rate
ET	Early termination
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
HbA1c	Glycated hemoglobin
hs-CRP	High-sensitivity C-reactive protein
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
JR	Joint replacement
K-L	Kellgren-Lawrence
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities

MMRM	Mixed-effect model repeated measure
MRI	Magnetic resonance imaging
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
PCSA	Potentially clinically significant abnormalities
PCSV	Potentially clinically significant value
PK	Pharmacokinetic
PT	Preferred term
Q4W	Every 4 weeks
RBC	Red blood cell
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Standard deviation
SNS	Sympathetic Nervous System
SOC	System organ class
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WBC	White blood cell
WHODD	WHO Drug Dictionary
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 strategy and statistical methods to be used in the analysis of data for study R475-OA-1758.

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 2, randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the neurological safety and efficacy of fasinumab compared to placebo in patients with pain due to Osteoarthritis (OA) of the hip or knee who have a history of inadequate pain relief for their OA pain from acetaminophen/paracetamol and a history of intolerance to or inadequate pain relief from oral Non-steroidal anti-inflammatory drugs (NSAIDs) and opioids (or are unwilling to take opioids) for OA pain management. This study will evaluate the neurological safety of fasinumab compared to placebo in OA patients treated for up to 16 weeks by measuring nerve conduction velocities and evoked amplitudes of the peroneal, ulnar, and sural nerves. This study will also provide additional safety, tolerability, efficacy, pharmacokinetic (PK), and immunogenicity data for fasinumab.

The target study population was chosen because they currently have unmet medical needs with respect to unacceptable pain control, in spite of the availability of current analgesic treatment options.

1.2. Study Objectives

1.2.1. Primary Objectives

The primary objective of the study is to evaluate the effect of fasinumab compared to placebo on peripheral nerves in patients with pain due to OA of the hip or knee.

1.2.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the efficacy of fasinumab compared to placebo in patients with pain due to OA of the hip or knee
- To evaluate the safety and tolerability of fasinumab compared to placebo in patients with pain due to OA of the hip or knee

- To characterize the concentrations of fasinumab in serum in patients with pain due to OA of the hip or knee

- To evaluate the immunogenicity of fasinumab in patients with pain due to OA of the hip or knee

1.2.3. Modifications from the Statistical Section in the Final Protocol

This SAP is based on Protocol R475-OA-1758 Amendment 2.

1.2.4. Revision History for SAP Amendments

N/A.

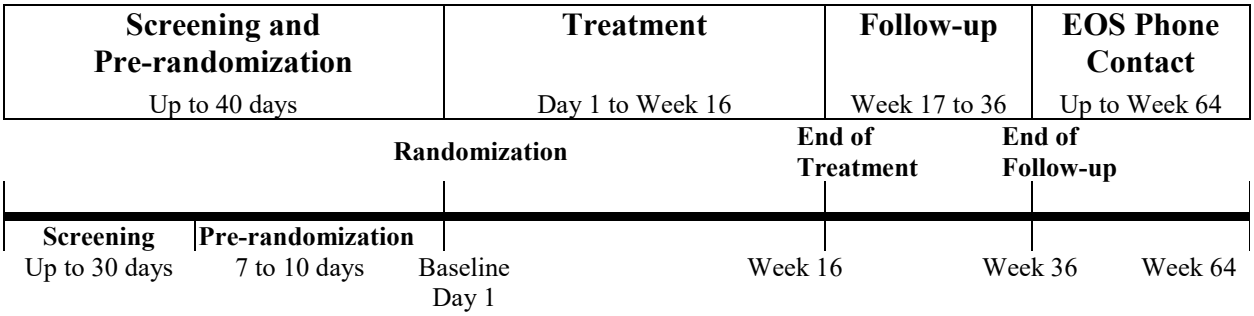
2. INVESTIGATION PLAN

2.1. Study Design and Randomization

This is a Phase 2, randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the neurological safety of fasinumab compared to placebo in patients with pain due to OA of the hip or knee. In addition, the safety, efficacy, PK, and immunogenicity of fasinumab compared to placebo will be assessed.

The study duration will be approximately 64 weeks starting at randomization (day 1). 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), a 20-week follow-up period, and an end of study (EOS) phone contact at 52 weeks following the last dose of study drug. See Figure 1 for the Study Flow Diagram.

Figure 1: Study Flow Diagram



EOS- End of study

Approximately 180 patients (90 patients per treatment group) will be recruited and randomized in a 1:1 ratio to the following treatment groups:

- Fasinumab 1 mg Subcutaneous (SC) Q4W
- Fasinumab-matching placebo SC Q4W

Randomization is stratified by the affected index joint (hip or knee) and by the Kellgren-Lawrence (K-L) score (2 to 3, or 4) at the screening visit.

2.2. Sample Size and Power Considerations

Approximately 180 patients will be randomized in a 1:1 ratio to fasinumab 1 mg Q4W or placebo. With this sample size, the precision of the estimated treatment difference between fasinumab and placebo at week 16 in nerve conduction velocity is no more than 1.21 m/s with a 95% confidence level, assuming a standard deviation (SD) of 3.6 m/s. This sample size provides similar precision for the estimated treatment difference in nerve conduction amplitude assuming

a SD of 3.6 µV. Assuming a 2-sided alpha level of 0.05 and a 15% dropout rate up to week 16, an enrollment of 90 patients per group will provide at least 80% power to detect an effect size of 0.46 in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and physical function subscale scores (ie, absolute treatment difference of 1.1 between fasinumab and placebo with an SD of 2.4). The assumed treatment difference and SD are based on results from study R475-PN-1227.

2.3. Study Plan

The Schedule of Events table is presented in Appendix 10.1.

3. ANALYSIS POPULATIONS

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

3.1. Full Analysis Set

The full analysis set (FAS) includes all randomized patients and is based on the treatment allocated (as randomized). Efficacy endpoints will be analyzed using the FAS.

3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized patients who received any study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

3.3. 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 result following the first dose of study drug.

3.4. Anti-Drug Antibody Analysis Set

The anti-drug antibody (ADA) analysis set includes all treated patients who received any study drug and had at least 1 qualified (non-missing) ADA result following the first dose of study drug. Patients will be analyzed according to the treatment actually received.

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, K-L 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, 65-74, >=75 years)
- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White, and Other)
- Ethnicity (Hispanic/Latino: Yes, No, Not Reported, and Unknown)
- Baseline Weight (kg)
- Baseline Height (cm)
- Baseline Body mass index (BMI) calculated from weight and height
- Index Joint (Knee or Hip) per IWRS
- K-L score (2, 3, 4) for the Index Joint
- K-L score for all Knees and Hips and severity for shoulders
- WOMAC pain score of the index joint at screening
- Duration of OA at baseline
- History of analgesic intolerance and inadequate pain relief
- Baseline nerve conduction variables measures

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 Medications

Medications/Procedures will be recorded from the day of informed consent until the end of follow-up period. 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 treatment period (as defined in Section 5.8) and ending during or after the treatment period.

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

4.4. Prohibited Medication

Patients will be required to discontinue all non-study pain medication (oral or topical; except up to 150 mg/day of aspirin/5-aminosalicylic acid [5-ASA], which is permitted for cardiac prophylaxis, per local guidelines), starting at the pre-randomization visit and through the treatment period.

Opioid analgesic medications (including tramadol) are prohibited through the week 16 study visit. Patients will be directed not to take concomitant medications that contain NSAIDs (oral or topical, except up to 150 mg/day of aspirin, which is permitted for cardiac prophylaxis) until at least 16 weeks after the last study drug injection.

Other prohibited medications during the treatment period include:

- Any other investigational agent
- Medical or regular recreational use of marijuana
- Chondroitin sulfate
- Glucosamine
- Hyaluronic Acid Intra-articular Injections
- Muscle relaxants including cyclobenzaprine, carisoprodol, orphenadrine, tizanidine (see protocol Section 7.7.2 for permitted muscle relaxants)

- Corticosteroids (topical, intranasal, and inhaled formulations are permitted), adrenocorticotropic hormone
- Cyclosporine, methotrexate, mycophenolate mofetil, tacrolimus
- Azathioprine, sulfasalazine, hydroxychloroquine
- Interleukin -6 or interleukin-6 receptor antagonists
- Abatacept, ustekinumab
- Tumor necrosis factor antagonists
- IL-1 inhibitors, including diacerein
- Apremilast, and tofacitinib

The following variables will be summarized for prohibited medications:

- Number and percentage of patients using at least one prohibited medication during the treatment period
- Number and percentage of patients using at least one prohibited medication during the follow-up period
- Number and percentage of patients with at least one prohibited NSAID use during the treatment period
- Number of days patients used prohibited medications during the treatment period
- Number of days patients used prohibited NSAID during the treatment period

4.5. Efficacy Variables

The efficacy endpoints are the secondary endpoints of the study:

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

4.6. Safety Variables

Patient safety will be assessed through the collection of nerve conduction measures (described in protocol Section 8.2.3.1), reported adverse events (AEs), clinical laboratory data, vital signs, Electrocardiogram (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.

4.6.1. Primary Safety Variables

The primary endpoints of the study are:

- Change from baseline to week 16 in peroneal motor nerve conduction velocity
- Change from baseline to week 16 in peroneal motor nerve action potential amplitude
- Change from baseline to week 16 in sural sensory nerve conduction velocity
- Change from baseline to week 16 in sural sensory nerve action potential amplitude
- Change from baseline to week 16 in ulnar sensory nerve conduction velocity
- Change from baseline to week 16 in ulnar sensory nerve action potential amplitude

4.6.2. Additional Safety Variables

Additional safety endpoints in this study include:

- Incidence of Adjudicated arthropathy (AA, as confirmed by an independent adjudication committee) through week 36
- Incidence of Destructive arthropathy (DA, as confirmed by an independent adjudication committee) through week 36
- Incidence of treatment-emergent adverse event (TEAEs) through week 16
- Incidence of SNS dysfunction (as diagnosed after consultation with an appropriate specialist, such as a neurologist and/or cardiologist) through week 36
- Incidence of peripheral sensory AEs that require a neurology or other specialty consultation through week 36
- Incidence of all-cause JR surgeries week 36
- Incidence of JRs at telephone survey approximately 52 weeks after last dose of study drug

4.6.3. Adverse Events and Serious Adverse Events

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 period. All AEs are to be coded to a PT and associated primary SOC according to the MedDRA® (the latest current available version).

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and

unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug. An AE also includes any worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug.

A SAE is an AE that is classified as serious according to the criteria specified in the protocol.

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

- the test result is associated with accompanying symptoms, and/or
- the test result requires diagnostic testing and medical/surgical intervention, and/or
- the test result leads to a change in dosing (outside of protocol-stipulated dose adjustments), discontinuation from study, significant additional concomitant drug treatment, or other therapy.

4.6.4. Adverse Events of Special Interest

Adverse events of special interest (AESI) are AEs (serious or non-serious) required to be monitored, documented, and managed in a pre-specified manner as described in the protocol. In this study, the AESI are listed below (as provided in the protocol):

- Adjudicated Arthropathy (as confirmed by adjudication) selected using an eCRF specific tick box on the AE page.
- Sympathetic nervous system dysfunction (as diagnosed after consultation with an appropriate specialist, such as a neurologist and/or a cardiologist) selected using an eCRF specific tick box on the AE page.
- Peripheral sensory AEs that require a neurology or other specialty consultation selected using an eCRF specific tick box on the AE page.
- Joint replacement surgery (defined as elective joint replacement surgery not due to new or worsening AE) using eCRF specific tick box on the AE page.

4.6.5. Laboratory Safety Variables

The clinical laboratory data consists of serum chemistry, hematology, urinalysis and urine electrolytes. Samples for laboratory testing will be collected at the time points specified in the Schedule of Events (Appendix 10.1).

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 10.2 for PCSV definitions).

4.6.6. Vital Signs

The following vital signs parameters will be collected according to the Schedule of Events in Appendix 10.1:

- Body temperature (ºC)
- Supine/standing systolic and diastolic blood pressures (mmHg) and pulse (bpm)
- Respiratory rate (breaths per minute)

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. PCSV ranges will be applied to the vital sign parameter values as applicable (see Appendix 10.2 for PCSV definitions).

4.6.7. 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.

4.6.8. 12-Lead Electrocardiography

A standard 12-lead ECG will be performed according to the Schedule of Events in Appendix 10.1. 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:

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

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.

PCSV ranges will be applied to the ECG parameter values as applicable (see Appendix 10.2 for PCSV definitions).

4.6.9. Physical and Neurological Examination Variables

Patients will have a thorough and complete physical examination including an examination of the knees, hips, and shoulders performed according to the Schedule of Events in Appendix 10.1. The result for each body system is an outcome of normal or abnormal (clinically significant, or not clinically significant). Neurological evaluations will cover the following domains: motor, sensory, cranial nerves, reflexes and coordination/balance and assessment for presence/absence of signs of carpal tunnel syndrome. The results of each specific domains will be described as normal or abnormal (clinically significant, or not clinically significant) with the exception of the carpal tunnel evaluation which will be described as present/absent.

4.6.10. Biomarker variables

Biomarker analysis will be described in a separate biomarker SAP.

4.6.11. Other Safety Variables

Other safety endpoints include:

- Survey of Autonomic Symptoms questionnaire:
  - The Survey of Autonomic Dysfunction serves as a monitoring tool throughout the study to prompt further evaluation of potential events of sympathetic nervous system dysfunction, as deemed necessary at the investigator's discretion. The survey asks if patients have a symptom, to what extent they are bothered by it.

The extent to which symptoms are bothersome are described in 5 categories (not at all, a little, some, moderate, a lot).

– Summaries will include the number and proportion of patients presenting with symptoms at scheduled timepoints by degree of bothersomeness. Change from baseline in the degree of bothersomeness of each symptom represented will also be presented at scheduled timepoints. Change from baseline in the degree of bothersomeness will be described as better, same or worse.

- 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 affected joints as well as other knee or hip joints at each scheduled visit (taken from bilateral x-rays).
- All-cause JR:
  - Number and percentage of patients with JR (all-cause JRs)
  - Reason for JR (all-cause JRs)
  - Time to JR (all-cause JRs)
- Adjudicated Arthropathy (AA):
  - Number and percentage of patients with AA
  - Number and percentage of patients meeting Destructive Arthropathy criteria (DA)
  - Subtypes of AA
  - Time to AA
  - Time to DA

4.7. Pharmacokinetic Variables

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

4.8. Anti-Drug Antibody Variables

The immunogenicity variables are ADA status, titer, at each time-point/visit. Serum samples for ADA will be collected at the clinic visits specified in Appendix 10.1.

5. STATISTICAL METHODS

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, median, SD, minimum, 1st & 3rd quartiles (Q1 & Q3), and maximum.

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

Period of Observation - Unless otherwise stated, analysis of all safety and non-safety variables captured at multiple visits will be analyzed by the following observation periods:

- The *Pre-Treatment Period* is defined as the time from signing the ICF to before the first dose of study drug.
- The *On-Treatment Period* is defined as the time from the first dose of study drug up to 28 days after the last dose of study drug.
- The *Follow-Up/Post-Treatment Period* is defined from the end of the On-Treatment Period to the date of the follow-up clinic visit (Week 36 visit) or early termination date.

5.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics described in Section 4.1 will be descriptively summarized by treatment group and overall for the study based on FAS.

5.2. Medical History

All reported patient's medical history and surgical history will be descriptively summarized by primary SOC and PT by treatment group and overall for the FAS. The tables will be sorted by decreasing frequency of primary SOC in the fasinumab group. Within each primary SOC, PTs will be sorted by decreasing frequency in the fasinumab group.

5.3. Prior/Concomitant Medications

Prior Medications

All prior medications, dictionary coded by WHO, will be descriptively summarized by treatment group based on the FAS. Summaries will present number and percentage of patients for all prior medications, by decreasing frequency of the fasinumab group incidence of ATC followed by ATC level 2, ATC level 4 and PT. 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 based on the SAF. Summaries will present number and percentage of patients for the concomitant medication groups described in Section 4.3 for all concomitant medications, by decreasing frequency of the fasinumab group incidence of ATC followed by ATC level 2, ATC level 4 and PT. 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.

5.4. Prohibited Medications

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

The number of patients with NSAIDs use during treatment period will be summarized by treatment group based on the SAF.

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

5.5. Subject Disposition

The disposition of patients in the study will be summarized by treatment group and overall for FAS. The following will be provided:

- The total number of screened patients: signed the Informed consent form (ICF)
- The total number of randomized patients: received a randomization number
- The total number of patients in each analysis set

- The total number of patients who discontinued the study, and the reasons for discontinuation
- The number of patients who completed study treatment, patients who discontinued treatment and reason for treatment discontinuation
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation
- A listing of patients who withdrew from the study, along with reasons for study withdrawal

5.5.1. Screening Disposition

In the summaries below, percentages will be calculated using the number of screened patients as the denominator. Summaries will present the overall frequencies (and percentages as applicable) for the following:

- Screened patients (defined as having signed the ICF).
- Patients randomized (defined in the protocol as having received a randomization number).
- Patients that did not meet the inclusion/exclusion criterion but were randomized (if applicable).
- Patients treated but not randomized (if applicable).
- Screen Fail patients: broken out by reason for screen failure.

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

- Listing of Patients Treated but not Randomized.
- Listing of Screening Failures and reasons for all screen failing

5.5.2. Treatment and Study Disposition

Unless otherwise noted, percentages will be calculated using the number of patients in the FAS as the denominator. Summaries will present the frequencies (and percentages as applicable) by treatment group for the following:

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

- Patients randomized and treated.
- Patients randomized but not treated. This row will reflect grouping based on randomization assignment.
- Patients who completed study treatment period.
- Patients who discontinued treatment, and reason for treatment discontinuation.
- Patients who completed the study.
- Patients who withdrew from the study, and reason for study withdrawal.

A Kaplan-Meier plot of time to treatment/study discontinuation by treatment group will be provided.

5.6. Extent of Study Treatment Exposure and Compliance

The analysis population is based on the SAF.

5.6.1. Treatment Compliance

Overall treatment compliance to the SC study drug injection is defined as the actual number of SC injections divided by the expected number of SC injections during the on-treatment period up to treatment discontinuation. It is calculated according to the following formula:

$$\frac{Number\ of\ actual\ injections\ of\ study\ drug\ received\ during\ the\ treatment\ expsoure\ period}{Number\ of\ planned\ injections\ of\ study\ drug\ during\ the\ treatment\ exposure\ period\ on\ or\ before\ the\ time\ that\ the\ patient\ discontinued\ from\ the\ treatment\ phase\ of\ the\ study} \ x\ 100$$

The total number of SC injections will be summarized by treatment groups via descriptive statistics based on the SAF. A summary of the number (and percentage) of patients categorized by the number of SC injections received will also be included.

5.6.2. Treatment Exposure

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

- (Date of last administration of study drug - date of the first study drug administration after randomization) + 28

The duration of exposure will be summarized for each treatment group by descriptive statistics.

The number and percentage of patients randomized and exposed to double-blind study drug will be presented by specific time periods for each treatment group. The time periods of interest are specified as: ≥ 1 day, ≥ 29 days, ≥ 57 days, ≥ 85 days and ≥ 113 days.

5.6.3. Length of Study Observation/Participation

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

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

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

- (Date of the last study visit [up to the EOS Phone Call] – date of the first study drug administration) + 1

The lengths of observations and total study participation will be summarized for each treatment group by descriptive statistics based on the SAF.

The number and percentage of patients with observation and participation 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, ≥ 183 days, ≥ 253 days, ≥ 449 days.

5.6.4. Protocol Deviations

All important and minor protocol deviations have been collected and reviewed on an ongoing basis throughout the study as described in the Protocol Deviation Plan.

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

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

5.7. Analysis of Efficacy Data

5.7.1. Efficacy Analysis

The secondary efficacy endpoints of the study are:

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

The following hypotheses will be tested:

- $H_{0,1}$: There is no treatment difference between fasinumab 1 mg Q4W and placebo in WOMAC pain subscale at week 16
- $H_{0,2}$: There is no treatment difference between fasinumab 1 mg Q4W and placebo in WOMAC physical function subscale at week 16

For the above hypotheses, the estimand is the difference in means between each fasinumab 1 mg Q4W and placebo in the change from baseline to week 16 in the WOMAC pain and physical function scores in the FAS, regardless of whether or not prohibited medication had been taken. Any data collected after discontinuing treatment will not be used in the main efficacy analysis, but used in a treatment policy sensitivity analysis.

Each of the secondary efficacy variables will be analyzed using a multiple imputation approach with mixed-effect model for repeated measure (MMRM) based on the FAS. For patients who permanently discontinued treatment due to lack of efficacy, death or AEs, their missing WOMAC subscale scores after discontinuation will be imputed with values centered at the mean baseline WOMAC subscale score of the treatment group that patient was randomized to. For patients who discontinued treatment due to other reasons, their missing WOMAC subscale scores after discontinuation will be imputed under missing-at-random assumption using the regression method with adjustment for covariates including treatment group, randomization strata (K-L category [2 to 3, or 4] and index joint [knee, hip]) and baseline WOMAC subscale score. Intermittently missing WOMAC subscale prior to treatment discontinuation will be imputed using Markov Chain Monte Carlo method.

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 4751758.

- Step 2: The missing WOMAC subscale scores at visits subsequent to treatment discontinuation will be imputed using the regression method for the monotone pattern with seed number 4751758 and adjustment for covariates including treatment groups, randomization strata (K-L category [2 to 3, or 4] and index joint [knee, hip), baseline WOMAC subscale score and all WOMAC subscale scores at preceding visits.

- Step 3: For patients who discontinued treatment due to lack of efficacy or AEs, the initially missing and now imputed WOMAC subscale scores at visits subsequent to treatment discontinuation 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 subscale 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 WOMAC subscale score, randomization strata (K-L category [2 to 3, or 4] and index joint [knee, hip]), treatment, visit, and treatment-by-visit interaction as fixed effects. Patients will be included as random effects. The MMRM will be fitted using the MIXED procedure in Statistical Analysis System (SAS) with an unstructured covariance matrix to model the within-patient errors. The denominator degrees of freedom will be estimated using Kenward-Roger's approximation. In the event a model cannot be fitted due to the estimation algorithm failing to converge, the covariance matrix for within-patient errors will be modeled by an autoregressive 1 structure, followed by a compound symmetry structure if convergence is still not achieved for the prior.

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

The null hypotheses will be rejected when the p-values corresponding to the difference in change from baseline to week 16 between fasinumab 1 mg Q4W and placebo is less than the available $\alpha_0 = 0.05$ for both the WOMAC pain subscale score and physical function subscale score.

For analysis of categorical variables, eg, proportions of patients with ≥30% or ≥50% improvement in the WOMAC pain subscale scores at week 16, 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 10.3), the Cochran Mantel Haenszel approach stratified by the randomization strata will be used with missing data considered as non-response.

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

Cumulative distribution of percent change from baseline in WOMAC pain and physical function subscale 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.

Sensitivity Analysis

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

Analysis of Treatment Policy Estimand

Sensitivity analysis of treatment policy estimand for the secondary endpoints will be performed using similar analysis method as the secondary efficacy analysis. The treatment policy estimand is the difference in means between each fasinumab and placebo in the change from baseline to week 16 in the WOMAC pain and physical function scores in the FAS, 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 analysis. Missing WOMAC subscale scores up to week 16 will be imputed using the same approach as in Section 5.7.1.

5.7.2. Subgroup Analysis

Descriptive analyses by treatment group will be performed on both raw and change from baseline values for each visit for the WOMAC pain subscale score and physical function

subscale scores to summarize the treatment effects across subpopulations defined by the following baseline characteristics:

- K-L category [2 to 3, or 4]
- Index joint [Knee, Hip]
- Age group [< 65, 65-74, >=75]
- Sex [Male, Female]
- Weight group [< Median, ≥ Median]
- BMI group [≤ Median, > Median]

Forest plots for the subgroup analysis will be provided.

5.7.3. Analysis of Other Efficacy Variables

Rescue Medications

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

Number of days patients used rescue medication during the treatment period (Day 1 to Week 1, Week 1 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.

For patients taking rescue medication, weekly average usage of rescue medications (measured in mg) is calculated as follows:

$$= \frac{Total\ amout\ of\ rescue\ medication\ used\ in\ the\ specified\ week\ (in\ mg)}{number\ of\ diary\ entries\ in\ the\ specified\ week}$$

Descriptive statistics of the weekly average usage of rescue medications will be presented by treatment group based on the FAS.

5.8. Analysis of Safety Data

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

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

Thresholds for Potential Clinically Significant Values (PCSV) in laboratory variables, vital signs and ECG are defined in Section 10.3.

The summary of safety results will be presented for each treatment group and by visit where applicable.

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 AEs, including AESIs (except JR identified at the 64-week telephone follow-up), or abnormalities is between the first dose of study drug dose up to the end of the Follow-Up Period (i.e., week 36/Early Termination). Any study drug-related SAEs occurring between the end of Follow-Up clinic visit and the EOS will also be included. Data collected outside this interval will be excluded from the descriptive statistics and identification of abnormalities for laboratory evaluations, ECGs and vital signs. All post-baseline data during the interval will be used in the PCSV analysis including scheduled and unscheduled assessments.

5.8.1. Primary Safety Analysis

The variables for the evaluation of peripheral nerve function are the change from baseline to week 16 (based on central reader assessment) in the amplitude and velocity from the 3 individual nerve conduction tests.

The nerve conduction variables will be analyzed using an MMRM approach based on the safety analysis set. The model will include baseline value, randomization strata, treatment, visit, and treatment-by-visit interaction. The least-squares mean estimates for the mean change from baseline to week 16, as well as the differences of the estimates between fasinumab and placebo, with their corresponding standard errors and associated 95% confidence intervals, will be provided descriptively.

No imputation will be made for Nerve Conduction values that were missing as a result of technical error, were not performed, or performed outside of scheduled visit windows. For measurements recorded as physiologically absent ("No Response", meaning outside detection sensitivity of the test), nonzero values were imputed using the 1st percentile of all non-missing values across all visits, all patients, and all treatment groups. This will be done to impute the low end of the range of detectable values while avoiding undue influence by outliers.

Data collected after discontinuing treatment up to week 16 will be included and used in the primary safety analysis. Any unscheduled repeated NCT tests data outside the window described in Section 6.6 will not be used in the primary safety analysis, but used in a sensitivity analysis.

Sensitivity Analysis

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

Sensitivity analysis for the primary safety endpoints will be performed using similar analysis method as the primary safety analysis. For the unscheduled repeated tests at week 8, week 16 and week 36, the window described in Section 6.6 won't be used. Alternatively, the last test value prior to the next scheduled visits will be used in this sensitivity analysis. Missing nerve

conduction variables up to week 16 will be imputed using the same approach used in the primary analysis.

5.8.2. Adverse Events

All AEs reported in this study will be coded using the currently available version of MedDRA®. Coding will be to lowest level terms. The verbatim text, PT, and SOC will be listed.

- *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 AEs that developed or worsened 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.

Post treatment AEs and all 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
  - Total number of AESIs
  - Patients with any TEAEs
  - Patients with any Serious TEAEs
  - Patients with any AESIs
  - 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
- TEAEs by SOC and PT
  - All TEAEs

  - TEAEs by severity: mild, moderate or severe
  - TEAEs resulting in permanent study treatment discontinuation
- Treatment-related TEAEs by SOC and PT
  - All treatment-related TEAEs
- TEAEs by PT
  - All TEAEs
  - TEAEs resulting in permanent study treatment discontinuation
- Post-treatment AEs by SOC and PT
  - All post-treatment AEs
  - Post-treatment AEs by severity: mild, moderate or severe
- Serious TEAEs by SOC and PT
- Post-treatment Serious AEs by SOC and PT
- All serious AEs on study by SOC and PT
- Non-serious TEAEs by SOC and PT
- Post-treatment non-serious AEs by SOC and PT
- All non-serious AEs on study by SOC and PT
- All AEs on study by SOC and PT
  - All AEs
  - All AEs by severity: mild, moderate or severe
- Death

Counts will be provided according to treatment group for each PT within each SOC. Percentages will be calculated using the number of patients in each treatment group using the respective SAF.

Primary SOCs will be sorted by decreasing frequency in the fasinumab group. Within each primary SOC, PTs will be sorted by decreasing frequency in the 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.

The following listings will be included:

- AEs leading to death
- TEAEs leading to permanent discontinuation from study drug (not applicable to post-treatment AEs)
- TEAEs leading to withdrawal from study
- Patients with Serious TEAEs
- AESIs
- Deaths
- All Joint Replacements
- All AEs
-

5.8.3. Adverse Events of Special Interest

Adverse events of special interest (AESI) include adjudicated arthropathies, AEs confirmed as SNS dysfunction as well as peripheral neurosensory events and joint replacements meeting pre-specified AESI criteria. AESIs will be flagged in the database using predefined tick boxes to denote the events.

Summaries of AESI incidence by treatment group will include:

- Incidence of adjudicated arthropathy events
- Incidence of adjudicated arthropathies that meet destructive arthropathy criteria
- Incidence of joint replacements AESI events
- Incidence of sympathetic nervous system dysfunction AESI events
- Incidence of peripheral neurosensory AESI events

5.8.4. Clinical Laboratory Measurements

Baseline clinical laboratory analytes and change from baseline in clinical laboratory analytes to each scheduled assessment time will be summarized with descriptive statistics for each treatment group.

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

A Treatment-Emergent PCSV is a laboratory value that was normal or abnormal but not meeting PCSV criteria at Screening and Baseline but became abnormal and met PCSV criteria after treatment with study drug. Definition of PCSV is listed in Appendix 10.2. Treatment-Emergent PCSVs will be summarized by treatment group.

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

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

- 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)

The above laboratory summaries will be constructed for the On-Treatment Periods. Lab data collected during the Pre-Treatment and Post-Treatment Periods will be displayed in listings.

5.8.5. Analysis of Vital Signs

Vital signs (temperature, blood pressure, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

A treatment-emergent PCSV is a vital sign value that was normal or abnormal but not meeting PCSV criteria at Screening and Baseline but became abnormal and met PCSV criteria after treatment with study drug. Definitions of PCSV is listed in Section 10.3. Treatment-Emergent PCSVs will be summarized by treatment group.

The incidence of confirmed measurements suggesting orthostatic hypotension will also be summarized by treatment group.

The above vital sign summaries will be constructed for the On-Treatment Period. Vital sign data collected during the Pre-Treatment and Post-Treatment Periods will be displayed in listings.

5.8.6. Analysis of 12-Lead Electrocardiography

ECG parameters (ventricular rate, Heart Rate, PR interval, QRS interval, QT interval and QTc interval) will be summarized by baseline and change from baseline to each scheduled assessment time.

A treatment-emergent PCSV is an ECG value that was normal or abnormal but not meeting PCSV criteria at Screening and Baseline but became abnormal and met PCSV criteria after treatment with study drug. Definitions of PCSV is listed in Section 10.3. Treatment-Emergent PCSVs will be summarized by treatment group.

ECG status (i.e. normal, abnormal not clinical significant or abnormal clinical significant) 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 group.

5.8.7. Physical and Neurological Examinations

The percentage of patients with new-onset clinically significant abnormal physical examinations will be summarized by treatment group showing frequency and percentage by body system for each period as well as at the end of the period. Similarly summaries will be presented for neurological exam findings. These summaries will be constructed for the on-treatment period, post-treatment period and overall during the study.

5.8.8. Joint Pain Questionnaire

The percentage of patients with worse joint pain will be summarized by visit and joint.

5.8.9. Analysis of Other Safety Variables

Other safety data includes the survey of Autonomic Symptoms, cases of AA and joint replacements.

Adjudicated Arthropathy

Adjudicated arthropathy events based on imaging data overall and by subtype will be summarized by treatment group based on the SAF. Incidence of AA (as confirmed by an independent adjudication committee) through week 36 will be summarized by treatment group based on the SAF. Time to first AA event will be summarized by Kaplan-Meier method if enough number of events occur. Cox regression model will be used for descriptively comparing each treatment group to placebo by obtaining hazard ratio estimates along with 95% confidence intervals. Swimmer plots depicting the length of the observation window per patient and indicating timepoints at which the initial event occurred, worsened and/or changed subtype category may be presented by treatment group.

Incidence of DA (as confirmed by an independent adjudication committee) through week 36 will be summarized by treatment group based on the SAF. Time to first DA event will be summarized by Kaplan-Meier method if enough number of events occur. Cox regression model

will be used for descriptively comparing each treatment group to placebo by obtaining hazard ratio estimates along with 95% confidence intervals.

All-cause joint replacements of any joint will be summarized by treatment group. The number of replacements in joints that were positively adjudicated will be summarized by treatment group. Joint replacements will also be summarized by KL score of the affected joint at screening.

In the time to event analyses, Time to first event will be calculated as: (Date of the first event – Date of the first dose of study drug +1). Patients without an event will be censored at the last visit for AA and DA in the analysis.

Survey of Autonomic Symptoms

The number of patients reporting the presence of each symptom/health problem assessed will be presented by treatment group at each scheduled visit. The number of symptoms reported and total symptom impact score will be presented by treatment group at each scheduled visit.

All-cause Joint Replacements

The number and percentage of patients with all-cause joint replacements will be presented by treatment group On-Treatment and Post-Treatment Periods based on the SAFs. The number of replacements in joints that were positively adjudicated will be summarized by treatment group. Joint replacements will also be summarized by KL score of the affected joint at screening. Additionally, the number and percentage of patients who reported joint replacements at the End of Study Phone Call will be summarized.

The time to JR is calculated as:

= (Date of JR – Date of first dose of study drug) + 1

5.9. Analysis of Pharmacokinetics and Drug Concentration Data

Summaries of concentrations of functional fasinumab will be presented by nominal time point and dose. Plots of individual concentration over time will be presented by actual day. Plots of mean or median concentration of functional fasinumab will be presented by dose and nominal day or week. No formal statistical analysis will be performed.

5.10. Analysis of Immunogenicity Data

5.10.1. Analysis of Anti-Drug Antibody Data

The immunogenicity variables described in Section 4.8 will be summarized using descriptive statistics. Immunogenicity will be characterized by ADA responses and titers observed in patients in the ADA analysis set. ADA response categories and titer categories are defined as follows:

ADA response categories

- ADA Negative, defined as ADA negative response at all time points, regardless of any missing samples.

- Pre-existing immunoreactivity, defined as either an ADA positive response in the ADA assay at baseline with all post first dose ADA results negative, OR a positive response at baseline with all post first dose ADA responses less than 9-fold over baseline titer levels.

- Treatment-emergent response, defined as a positive response in the ADA assay post first dose when baseline results are negative or missing. The treatment-emergent responses will be further characterized as Persistent, Indeterminate or Transient:
  - Persistent Response - Treatment-emergent ADA positive response with two or more consecutive ADA positive sampling time points, separated by at least 16-week period (based on nominal sampling time), with no ADA negative samples in between, regardless of any missing samples.
  - Indeterminate Response - Treatment-emergent ADA positive response with only the last collected sample positive in the ADA assay, regardless of any missing samples.
  - Transient Response - Treatment-emergent ADA positive response that is not considered persistent or indeterminate, regardless of any missing samples.
- Treatment-boosted response, defined as a positive response in the ADA assay post first dose that is greater than or equal to 9-fold over baseline titer levels, when baseline results are positive.

Titer categories (Maximum titer values)

- Low (titer <1,000)

- Moderate (1,000≤ titer ≤10,000)

- High (titer >10,000)

The following analysis will be provided:

- Number (n) and percent (%) of ADA-negative patients (pre-existing immunoreactivity or negative in the fasinumab ADA assay at all time points) by treatment groups

- Number (n) and percent (%) of treatment-emergent ADA positive patients by treatment groups and ADA titer categories

  - Number (n) and percent (%) of persistent treatment-emergent ADA positive patients

- Number (n) and percent (%) of indeterminate treatment-emergent ADA positive patients Number (n) and percent (%) of transient treatment-emergent ADA positive patients
- Number (n) and percent (%) of treatment-boosted ADA positive patients by treatment groups and ADA titer categories

Listing of all ADA titer levels will be provided for patients with pre-existing, treatment-emergent and treatment-boosted ADA response.

5.10.2. Association of Immunogenicity with Exposure, Safety and Efficacy

5.10.2.1. Immunogenicity and Exposure

Potential association between immunogenicity variables and systemic exposure to fasinumab will be explored by treatment groups. Plots of fasinumab concentration may be provided for analyzing the potential impact of ADA response status and titer on PK.

5.10.2.2. Immunogenicity and Safety and Efficacy

Potential association between immunogenicity variables and safety may be explored with a primary focus on the following safety events during the TEAE period:

- Injection site reaction (serious or severe and lasting 24 hours or longer)
- Hypersensitivity (SMQ: Hypersensitivity [Narrow])
- Anaphylactic Reaction (SMQ: Anaphylactic Reaction [Narrow])

Potential association between immunogenicity variables and efficacy and safety endpoints may be explored (e.g. scatter plot or spaghetti plot). The above-mentioned safety and efficacy analyses will be conducted using the following categories:

- ADA positive patients, that is patients with treatment-emergent or treatment-boosted response.
- ADA negative patients, that is patients with pre-existing immunoreactivity or negative in the ADA assay at all time points.
- Patients with persistent treatment-emergent ADA response.
- Maximum post-baseline titer in treatment-emergent or treatment-boosted ADA positive patients:
  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤ 10,000)

- High (titer >10,000)

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

Rules for handling missing data for efficacy assessments due to missing individual item data will follow each questionnaire's instrument manual. 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.

Due to public health measures implemented to address the world-wide COVID-19 pandemic, some sites may suspend onsite study visits or patients may opt not to attend. To mitigate data loss, patients may be contacted via telephone and the results of their efficacy measures transcribed verbally and entered into the eCOA devices. For analysis purposes, this data will be treated the same as efficacy data collected in an onsite visit and will be utilized in the efficacy analyses. Since all patients already had chance to complete week 16 visit prior to COVID-19 pandemic, there is no impact to the main efficacy endpoints and primary safety endpoints at week 16.

Data collected through the implementation of new CRFs regarding the impact of the COVID-19 pandemic (e.g. discontinuation due to COVID-19) on the patients will be summarized including missing visits, doses, and reason.

6.3. Data Handling Convention for Repeat Data

Orthostatic Hypotension data

This applies specifically to the data handling of repeat measurements in the assessment of orthostatic hypotension. Per protocol, if the initial vital assessment for orthostatic hypotension is consistent with the definition of orthostatic hypotension, the supine, standing blood pressure or pulse should be repeated up to 2 more times. The guideline for the repeat assessments are shown below:

Initial Assessment	Repeat Assessment 1	Repeat Assessment 2	Does patient meet OH criteria	Value to be used in the analysis
Does not meet OH definition	N/A	N/A	No	Initial Assessment
Meets OH definition - repeat	Does not meet definition - repeat	Does not meet definition	No	N/A
Meets OH definition - repeat	Does not meet definition - repeat	Meets OH definition	Yes, AE of OH reported	Repeat Assessment 2
Meets OH definition - repeat	Meets OH definition	N/A	Yes, AE of OH reported	Repeat Assessment 1

Baseline for the assessment of orthostatic hypotension vital assessments uses the last available assessment prior to the start of study drug. Measurements post-baseline will not be averaged. Rather frequency counts for patients meeting OH criteria for orthostatic hypotension will reflect the scenario as shown on the table.

Patient reported outcomes data

Should there be duplicate entries for patient reported outcomes data (not including diary data), the average of the entries will be used for questionnaires with numerical values such as the WOMAC. The worst category will be used in the analysis for questionnaires with categorical responses such as the SAS and Joint Pain Questionnaire.

6.4. Data Handling Convention for Missing Data

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

Imputation of AE and Concomitant Missing and Partial start dates:

Every effort will be made to collect the start dates of all AEs and concomitant medications. However, in the case the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the first dose of study medication, except if an incomplete date (e.g., month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the first dose of study medication date, then the start date of the first dose will be imputed, otherwise, the missing day or month by the first day or the first month will be imputed.

Imputation of Partial AE and concomitant Medication Partial end dates:

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.

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.

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.

Handling of missing item data for WOMAC

WOMAC scores will be computed when one pain, one stiffness, or 1-3 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.

Laboratory Safety Variables below lower limit of quantification (LLOQ)

For central laboratory data below the lower limit of quantification, 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 (PCSA)

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.

Date of first/last injection

Date of first injection is the first non-missing start date of dosing filled in the 'SC Study drug Injection" CRF module.

If a patient's date of the last dose is totally missing or unknown, his/her last visit date in the treatment period will be substituted.

6.5. Visit Windows

By-visit analysis (including 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 CRF assessment recorded by the investigator. For assessments without a nominal visit number such as Unscheduled, End of treatment (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 Table 1 Schedule of Events.

The following visit windows will be used to map all the visits for eCOA data (including WOMAC, Joint Pain Questionnaire and Survey of Autonomic System) and the unscheduled visits, early EOT visits, early study termination visits for other data, 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	Day -10 to -7	-10 to -1
3	Baseline	1	≤ 1
4	Week 1	8	[2, 11]
5	Week 2	15	[12, 22]
4	Week 4	29	[23, 43]
5	Week 8	57	[44, 71]
6	Week 12	85	[72, 99]
7	EOT Week 16	113	[100, 148]

8	Week 26	183	[149, 218]
12	Week 36	253	[219, 351]
13	Week 64	449	≥352

*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.

6.6. Nerve Conduct Test Analysis Windows

Per protocol, if the repeated per-protocol nerve conduction test performed on the regions of the peroneal, sural, or ulnar nerves at any post-baseline visit shows a difference from baseline of >12%, up to 2 unscheduled tests will be repeated at the same nerve.

The following visit windows will be used to map the unscheduled visits of the unscheduled NCT tests, based on the study day:

Visit	Targeted Study Days*	NCT Analysis Window in Study Days
Screening	Day -30 to Day -11	≥ -30 and ≤ -11
Pre-randomization	Day -10 to -7	-10 to -1
Baseline	1	≤ 1
Week 8	57	[29, 85]
EOT Week 16	113	[86, 183]
Week 36	253	≥184

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

If multiple measurements occur within the same visit window, the last one within the window will be used in the analysis.

6.7. Unscheduled Assessments

The determination of baselines and values at the EOT for both efficacy and safety variables will be based on scheduled available assessments and unscheduled available assessments.

Extra assessments (laboratory data or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing AEs) will be included in listings, but not

summaries. If more than 1 laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.

7. INTERIM ANALYSES

No interim analysis will be performed for primary safety and efficacy endpoints. For the first DBL, all patients have had the chance to complete the 16-week treatment period but some patients have not completed the 36-week follow-up period. All data up to the first DBL cutoff date will be included in the analysis.

8. SOFTWARE

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

9. REFERENCES

1. ICH. (1998, February 5). ICH Harmonized tripartite guideline: Statistical principles for clinical trials (E9). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

2. Joseph C Arezzo, et.al. (2008, September 16). Efficacy and safety of pregabalin 600 mg/d for treating painful diabetic peripheral neuropathy: A double-blind placebo-controlled trial. BMC Neurology 2008, 8:33.

10. APPENDIX

10.1. Schedule of Events

Study assessments and procedures are presented by study period and visit in Table 1.

Table 1: Schedule of Events

	Screening/Pre-randomization		Treatment Period								Follow-up Period			EOS
Study Week	**Screen**	**Pre-rand**	**Baseline**	**Wk 1**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**EOT Wk 16**	**ET[1]/ JR Pre-Op**	**Wk 26**	**Wk 36**	**ET[1] /JR Pre-Op**	**Wk 64**
Study Day	**Up to 30 Days**	**7 to 10 Days**	**1**	**8**	**15**	**29**	**57**	**85**	**113**		**183**	**253**		**449**
Visit Window (days)				**±1**	**±3**	**±7**	**±7**	**±7**	**±7**		**±7**	**±7**		**±7**
Visit/Phone Contact Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**		**Visit 10**	**Visit 11**		**Phone 1**
Screening/Baseline:														
Inclusion/Exclusion[2]	X	X	X											
Main study informed consent	X													
Genomics sub-study informed consent[3]	X													
Medical history	X													
Medication history	X													
Demographics	X													
Diary instructions		X	X											
Training on pain reporting /patient education brochures [4]	X	X												
MRI for index joint, contralateral joint & any hip or knee with K-L ≥3	X													
Randomization			X											
Treatment:														
Discontinue non-study pain medications		X												
Study drug SC injection[5]			X			X	X	X						

	Screening/Pre-randomization		Treatment Period								Follow-up Period			EOS
Study Week	**Screen**	**Pre-rand**	**Baseline**	**Wk 1**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**EOT Wk 16**	**ET[1]/ JR Pre-Op**	**Wk 26**	**Wk 36**	**ET[1] /JR Pre-Op**	**Wk 64**
Study Day	**Up to 30 Days**	**7 to 10 Days**	**1**	**8**	**15**	**29**	**57**	**85**	**113**		**183**	**253**		**449**
Visit Window (days)				**±1**	**±3**	**±7**	**±7**	**±7**	**±7**		**±7**	**±7**		**±7**
Visit/Phone Contact Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**		**Visit 10**	**Visit 11**		**Phone 1**
Dispense to home paracetamol/ acetaminophen		X	X			X	X	X						
Paracetamol/ acetaminophen accountability			X		X	X	X	X	X	X				
Record rescue medication use in diary[6]		X	X	X	X	X	X	X	X	X				
Concomitant therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient-Completed Assessments/Efficacy:														
WOMAC[7, 22]	X[7]		X		X	X	X	X	X	X	X	X	X	
Neurological Assessments:														
Nerve conduction	X[8]						X		X	X[9]		X	X[9]	
Neurological examination (full)	X		X		X	X	X	X	X	X	X	X	X	
Survey of autonomic symptoms[22]	X		X		X	X	X	X	X	X	X	X	X	
Orthostatic blood pressure assessment and heart rate [10,11]	X	X	X		X	X	X	X	X	X	X	X	X	
Safety:														
Vital signs[11]	X		X		X	X	X	X	X	X	X	X	X	
Electrocardiogram	X								X	X				
Physical examination and weight	X								X	X		X	X	
Joint pain questionnaire[22]	X		X		X	X	X	X	X	X	X	X	X	
Event-triggered imaging[12]				X	X	X	X	X	X	X	X	X	X	
Adverse Events	----------→													
SC injection site evaluation			X			X	X	X						

	Screening/Pre-randomization		Treatment Period								Follow-up Period			EOS
Study Week	**Screen**	**Pre-rand**	**Baseline**	**Wk 1**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**EOT Wk 16**	**ET[1]/ JR Pre-Op**	**Wk 26**	**Wk 36**	**ET[1] /JR Pre-Op**	**Wk 64**
Study Day	**Up to 30 Days**	**7 to 10 Days**	**1**	**8**	**15**	**29**	**57**	**85**	**113**		**183**	**253**		**449**
Visit Window (days)				**±1**	**±3**	**±7**	**±7**	**±7**	**±7**		**±7**	**±7**		**±7**
Visit/Phone Contact Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**		**Visit 10**	**Visit 11**		**Phone 1**
Bilateral X-rays (knee, hip, shoulder)	X[13]								X	X		X	X	
Pre-op questionnaire (JR follow-up)[14]										X			X	
MRI affected joint(s) - AA patients only[15]														X
End of study phone contact[16]														X
Laboratory Testing:														
Urine drug test[17]	X													
Hematology[17]	X					X		X	X	X	X	X	X	
Blood chemistry[17]	X					X		X	X	X	X	X	X	
Urinalysis and urine electrolytes[17]	X					X		X	X	X	X	X	X	
ESR	X													
HbA1c[17]	X													
FSH and estradiol[17,18]	X													
Pregnancy test (for WOCBP)[19]	X - Serum		X - Urine			X - Urine	X - Urine	X - Urine	X - Urine	X – Urine	X - Urine	X – Urine	X – Urine	
PK, Antibody, and Research Samples:														
PK sample[20]			X	X	X	X	X	X	X	X		X	X	
ADA samples[20]			X						X	X		X	X	
Genomics sub-study sample (optional)[3]			X											
hs-CRP sample[20,21]			X			X			X	X		X	X	
Research serum/plasma sample[20,21]			X			X			X	X		X	X	

AA: Adjudicated arthropathy
ADA: Anti-drug antibody
EOS: End of study
EOT: End of treatment
ESR: Erythrocyte sedimentation rate
ET: Early termination
FSH: Follicle stimulating hormone
JR: Joint replacement
MRI: Magnetic resonance imaging
PK: Pharmacokinetic
Pre-op: Pre-operative
Pre-rand: Pre-randomization
SC: Subcutaneous
Wk: Week

HbA1c: Glycated hemoglobin
hs-CRP: high-sensitivity C-reactive Protein
WOCBP: Women of childbearing potential
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Footnotes for Table 1 - Schedule of Events

1. Patients who discontinue study drug will be encouraged to follow the visit schedule throughout the entire study. If a patient chooses to end study participation he/she will be asked to return to the study site as soon as possible for an Early termination (ET) visit. Imaging assessments need to be repeated if it has been >30 days since the joints were last imaged. If it has been ≤30 days since imaging assessments were completed, imaging assessments may be completed at the discretion of the investigator.

2. 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. Patients must complete all other inclusion/exclusion assessments before undergoing the nerve conduction assessments.

3. Only for patients who provide written informed consent for the optional genomics sub-study. The sample should be collected at the day 1 (baseline/randomization) visit, but may be collected at any visit during the study after a patient has been randomized.

4. At the screening and pre-randomization visits, study staff will review the "Participating in a Research Study: What You Need to Know" brochure and the "Reporting Your Pain" brochure with patients to ensure they understand what a clinical study is and how to report their pain accurately. At subsequent visits, patients will be asked to review the 'Reporting Your Pain' brochure themselves. At any time during the conduct of the study, patients may require retraining by study staff.

5. Study drug administration will be the last procedure at each dosing visit, and will be administered after all laboratory, PK, ADA, and research samples have been collected and all study related activities have been performed. Patients will be observed in the clinic for approximately 1 hour after SC study drug is administered.

6. Use of study-provided rescue medication will be recorded daily using diaries. Acetaminophen/paracetamol use will be reported from pre-randomization visit to week 16.

7. The WOMAC pain sub-scale will be evaluated for both knees and both hip joints at the screening visit only. Then, the WOMAC Full Survey will be completed only for the index joint at the subsequent visits.

8. Nerve conduction can be performed during screening or pre-randomization. Patients must complete all other inclusion/exclusion assessments before undergoing the nerve conduction assessments. Randomization cannot occur until there is confirmation from the central reader assessment that the results are within the established parameters.

9. Nerve conduction assessments should be performed at the ET visit if it has been >2 weeks since the last nerve conduction assessment.

10. Blood pressure measurements to assess for orthostatic hypotension may be discontinued following regulatory approval if the safety database does not reveal an imbalance for the fasinumab-treated patients.

11. If the pulse is less than 45 bpm at any visit, an ECG with rhythm strip will be obtained and sent to the central reader to confirm the heart rate and rhythm.

12. Imaging (X-ray and/or MRI) will be performed at the investigator's discretion on any joint with worsening or exacerbation of pain beyond the fluctuations in pain typical for that patient's OA. This imaging will be submitted to the adjudication committee for review.

13. If screening radiographs are inconclusive for potential joint related findings, an MRI must be performed. Confirmation from the central reader that there are no exclusionary findings on the MRI must be received before a patient can be randomized.

14. In the event that a patient must undergo JR surgery during the study, the patient must complete the pre-operative visit (ET assessments, as applicable) and the procedures outlined in the schedule of events for JR follow-up. This will include a Knee Society Score questionnaire for knee replacements or Harris Hip Score questionnaire for hip replacements. The pre-operative visit must be completed before the JR surgery. Pre-operative images will be submitted to the adjudication committee for review.

15. If the AA joint(s) has undergone JR, an X-ray may be substituted for an MRI.

16. The purpose of this phone contact is to ask the patient if he/she has had or is scheduled (or on a waiting list) to have JR surgery. Pre-operative images will be submitted to the central reader for adjudication, if available.

17. Samples will be analyzed by the central laboratory and results will be evaluated by the investigator.

18. Assessment of FSH and estradiol levels are only to be performed if assessment of postmenopausal status is required (ie, for female patients ≤59 years of age).

19. In the event of a positive urine pregnancy test result, the patient must have a serum pregnancy test with a negative result in order to continue study drug. If the serum pregnancy test is positive, the patient must be withdrawn from study drug and should be asked to return to the clinic for all remaining study visits per the visit schedule.

20. Collection of samples for PK, ADA, and research are mandatory at the time points specified above. In addition, PK, ADA, and research samples may be drawn at any scheduled visit or unscheduled visit if a patient experiences a treatment-related safety TEAE. Samples should be collected prior to study drug administration on study drug dosing days.

21. Biomarker samples should be collected after the patients have been fasting overnight or for 8 hours (in the event of an afternoon visit).

22. Patient-reported outcome measures should be completed before any clinical assessments.

Table 2: Follow-up Period for Patients Undergoing Joint Replacement Surgery on Study

	Post-Operative	**Long-Term**
	Follow-up Visit 1 4 weeks after joint replacement surgery	**Follow-up Visit 2** 20 weeks after joint replacement surgery
Follow-up Study Day (Visit Window)[1]	**Follow-up Day 29 (±5)**	**Follow-up Day 140 (±7)**
Treatment:		
Concomitant medications and therapy	X	X
Safety:		
Adverse events	----------→	
Vital signs	X	X
Orthostatic blood pressure[2]	X	X
Physical examination with joint examination	X	X
Medical history related to the joint replacement	X	X
Joint pain questionnaire	X	X
Post-operative questionnaire[3]	X	X
Bilateral X-rays (shoulders, hips, knees)[4]	X[5]	X
Event-triggered imaging[6]	X	X

Footnotes for Table 2 - Follow-up Period for Patients Undergoing Joint Replacement Surgery

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. If it is not possible to obtain orthostatic blood pressure following JR then blood pressure and pulse should be recorded.

3. A Knee Society Score questionnaire for knee replacements or Harris Hip Score questionnaire for hip replacements.

4. 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.

5. Imaging will be done at week 4 if not done pre-operatively.

6. Imaging may be performed on any joint following a report of clinically significant worsening or exacerbation of pain in that joint.

10.2. 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 3: 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

Parameter	Treatment Emergent PCSV	Comments
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.
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.

Parameter	Treatment Emergent PCSV	Comments
CPK*	>3 and ≤ 10 ULN and baseline ≤ 3ULN*	FDA Feb 2005.
	>10 ULN and baseline ≤ 10ULN	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
Creatinine	≥150 µmol/L (Adults) and baseline < 150 µmol/L	Benichou C., 1994
	>=30% change from baseline and <100% change from baseline	3 independent criteria
	≥100% change from baseline	
Uric Acid		Harrison - Principles of internal Medicine 17th Ed., 2008.
Hyperuricemia	>408 µmol/L and <=408 µmol/L at baseline	Two independent criteria
Hypouricemia	<120 µmol/L and >= 120 µmol/L at baseline	
Blood Urea Nitrogen	≥17 mmol/L and <17 mmol/L at baseline	Two independent criteria

Parameter	Treatment Emergent PCSV	Comments
Chloride		Two independent criteria
Hypochloremia	<80 mmol/L and baseline ≥ 80 mmol/L	
Hyperchloremia	>115 mmol/L and baseline ≤ 115 mmol/L	
Sodium		Two independent criteria
Hyponatremia	≤129 mmol/L and baseline > 129 mmol/L	
Hypernatremia	≥160 mmol/L and baseline <160 mmol/L	
Potassium		FDA Feb 2005.
Hypokalemia	<3 mmol/L and baseline ≥ 3 mmol/L	Two independent criteria
Hyperkalemia	≥5.5 mmol/L and baseline <5.5 mmol/L	
Total Cholesterol	≥7.74 mmol/L and < 7.74 mmol/L at baseline	Threshold for therapeutic intervention.
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	

Parameter	Treatment Emergent PCSV	Comments
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) ≥16.0 Giga/L and < 16 Giga/L at baseline	Increase in WBC: not relevant. 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); <1.0 Giga/L and >=1.0 Giga/L at baseline (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L <= 0.7 Giga/L at baseline	
Basophils	>0.1 Giga/L <= 0.1 Giga/L at baseline	
Eosinophils	(>0.5 Giga/L and >ULN) and (<=0.5 Giga/L or <= ULN at baseline)	Harrison - Principles of internal Medicine 17th Ed., 2008.

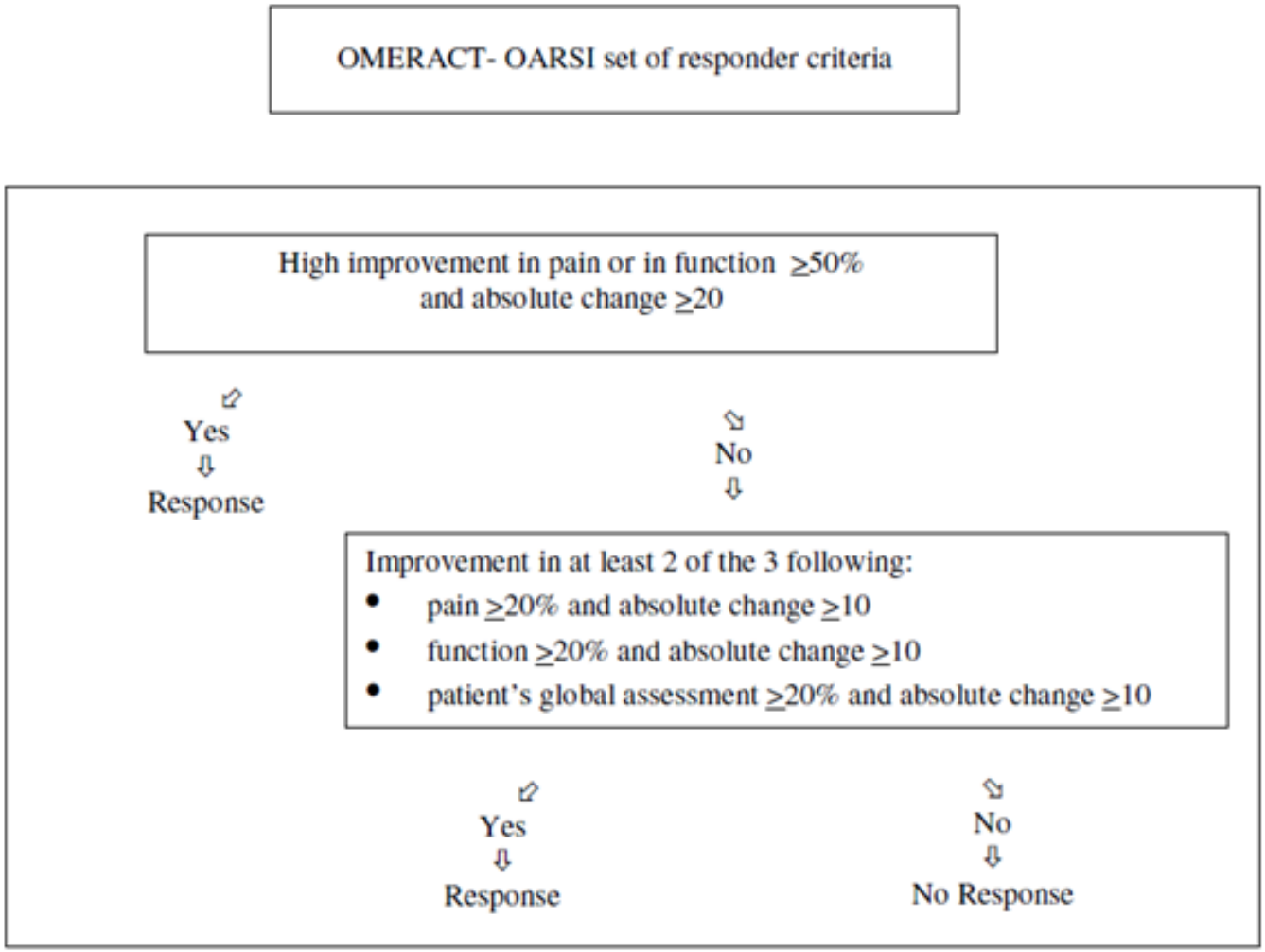
Parameter	Treatment Emergent PCSV	Comments
Hemoglobin	≤115 g/L and > 115 g/L at baseline for male; ≤95 g/L and> 95 g/L at baseline for Female. ≥185 g/L and <185 g/L at baseline for Male; ≥165 g/L and < 165 g/L at baseline for Female Decrease from Baseline ≥20 g/L	Three criteria are independent. Criteria 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.

Parameter	Treatment Emergent PCSV	Comments
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
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.

Parameter	Treatment Emergent PCSV	Comments
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.
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	

Parameter	Treatment Emergent PCSV	Comments
QTc	Absolute values (ms)	To be applied to any kind of QT correction formula.
	>450 ms and baseline <=450 ms	
	>480 ms and baseline <=480 ms	
	>500 ms and <= 500 ms at baseline	
	Increase from baseline	ΔQTc>60 ms are the PCSA to be identified in individual subjects/patients listings.
	Increase from baseline 30-60 ms	
	Increase from baseline >60 ms	

10.3. 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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ESig Approval	[redacted]20 13:55:06 GMT+0000

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