STATISTICAL ANALYSIS PLAN

VERSION: FINAL

A PHASE 3 RANDOMIZED, DOUBLE-BLIND, MULTI-DOSE, PLACEBO AND NSAID-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF FASINUMAB IN PATIENTS WITH PAIN DUE TO OSTEOARTHRITIS OF THE KNEE OR HIP

Compound:	REGN475 (fasinumab)
Protocol Number:	R475-OA-1688
Clinical Phase:	Phase 3
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatistician:	[redacted]
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Study Medical Director:	[redacted]
Version/Date:	Original Statistical Analysis Plan / 08April 2020

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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AA	Adjudicated Arthropathy
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CI	Confidence Interval
DA	Destructive Arthropathy
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EQ-5D	EuroQol Group Questionnaire
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
ICF	Informed consent form
ICH	International Conference on Harmonization
IVRS	Interactive Voice Response System
JR	Joint replacement
K-L	Kellgren-Lawrence
LS	Least Squares
MedDRA®	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model for repeated measures
MRI	Magnetic resonance imaging
NGF	Nerve growth factor
NRS	Numeric Rating Scale
NSAIDs	Nonsteroidal anti-inflammatory drugs
OA	Osteoarthritis
OMERCAT-OARSI	Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative and The Outcome Measure in Rheumatology
PCSV	Potentially clinically significant value
PK	Pharmacokinetic
PPS	Per protocol set
PT	Preferred term

Q4	Every 4 (weeks)
Q8	Every 8 (weeks)
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
RPOA	Rapidly Progressive Osteo-Arthritis
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SC	Subcutaneous
SD	Standard deviation
SF-36	Short Form (36) Health Survey
SOC	System organ class
TEAE	Treatment-emergent adverse event
TJR	Total joint replacement
ULN	Upper limit of normal
WBC	White blood cell
WOMAC	Western Ontario and McMaster 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 R475-OA-1688 study.

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 data lock and before code breaking.

1.1. Background/Rationale

This randomized, double-blind, placebo- and NSAID-controlled study is designed to evaluate the efficacy and safety of fasinumab in patients with OA of the knee or hip who have a history of inadequate pain relief from acetaminophen/paracetamol and a history of intolerance to or inadequate pain relief from opioids (or are unwilling to and/or lack access to take opioids) for OA pain management. This study will compare the efficacy and safety of fasinumab to placebo and to a pooled NSAID group of celecoxib or diclofenac, which are members of the class of NSAID medications commonly used for moderate-to-severe pain due to OA.

The target study population was chosen because they currently have unmet medical needs with respect to incomplete pain control, despite the availability of NSAIDs i.e. they have failed or are intolerant to opioids and have failed acetaminophen/paracetamol and thus provides equipoise with regards to randomization of patients to fasinumab or placebo. Patients were also required to be on a stable dose of NSAID, defined as oral NSAID use at regularly prescribed doses for approximately 4 days per week over the last 4 weeks prior to the start of the screening period.

This study will provide efficacy and safety data for OA patients exposed for up to 24 weeks to fasinumab, a pooled NSAID comparator group (celecoxib or diclofenac), or placebo.

1.2. Study Objectives

1.2.1. Primary Objectives

The primary objective of the study is to evaluate the efficacy of fasinumab compared to placebo, when administered for up to 24 weeks in patients with pain due to OA of the knee or hip.

1.2.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the efficacy of fasinumab compared to NSAIDs, when administered for up to 24 weeks in patients with pain due to OA of the knee or hip
- To assess the safety and tolerability of fasinumab compared to placebo and compared to NSAIDs, when administered for up to 24 weeks in patients with pain due to OA of the knee or hip

- To characterize the concentrations of fasinumab over time when administered for up to 24 weeks in patients with pain due to OA of the knee or hip
- To evaluate the immunogenicity of fasinumab administered for up to 24 weeks in patients with pain due to OA of the knee or hip

1.2.3. Exploratory Objectives

- To evaluate patient-reported outcome measures in patients with pain due to OA of the knee or hip treated for up to 24 weeks with fasinumab compared to placebo and compared to NSAIDs
- To evaluate the use of rescue medication in patients with pain due to OA of the knee or hip treated for up to 24 weeks with fasinumab compared to placebo and compared to NSAIDs

1.2.4. Modifications from the Statistical Section in the Final Protocol

This SAP is based on Protocol R475-OA-1688 Amendment 4. The following were modified or were not specified in the protocol but are being clarified/added in this SAP:

- The Per-protocol set (PPS) was updated to exclude patients with relevant protocol deviations rather than major protocol deviations as stated in the protocol since not all major/important protocol deviations will lead to removal of patients from the PPS.
- The Urgent Safety Measure Set (USMS) was explicitly defined in this SAP since the protocol intimates that USM patients will not be included as part of the full analysis set (FAS).
- The Neutralizing Anti-Body (Nab) Set was included to support the ADA analysis that is planned to be performed.
- Subgroup analyses for the change from baseline in WOMAC pain subscale and physical function subscale scores at week 24 by flare status. Flare patients are defined as patients who experience a ≥ 1 point increase in WOMAC pain scores from the Screening to the Baseline Visit.
- Analyses for the percentage of patients who had improvements of ≥ 50% and ≥ 70% in the WOMAC pain subscale scores at week 24
- Analyses for the percentage of patients who had improvements of ≥30%, ≥ 50% and ≥ 70% in the WOMAC physical function subscale scores at week 24
- Analyses for the percentage of patients who met the OMERACT-OARSI criterion at week 24. The OMERACT-OARSI criterion are described in Appendix Section 10.5 of this SAP.
- Analyses for additional exploratory endpoints of change in WOMAC pain and physical function subscale scores from baseline to the average score across Weeks 12, 16, 20 and 24.

1.2.5. Revision History for SAP Amendments

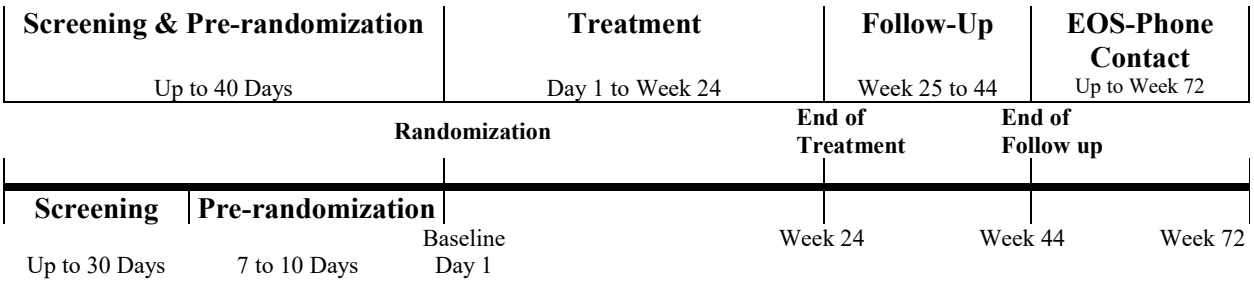
None.

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

This study is a randomized, double-blind, placebo- and NSAID-controlled study designed to evaluate the efficacy and safety of fasinumab in patients with OA of the knee or hip who have a history of inadequate pain relief with acetaminophen/paracetamol and a history of intolerance to or inadequate pain relief with opioids (or are unwilling to take opioids or have lack of access to opioids). The study consists of a screening period of up to 30 days, a 7 to 10 day pre-randomization/washout period (7 days with a +3 day window), a 24-week treatment period (with the last Q4W dose of study drug administered at week 20), a 20-week follow-up period, and a final phone call approximately 52 weeks after the last SC dose of study drug (Figure 1).

Figure 1: Study Flow Diagram



EOS- End of study

Patients will be randomized on day 1 (baseline) to one of the following treatment groups:

- Fasinumab 1 mg SC Q4W and NSAID-matching placebo oral, twice daily
- Fasinumab-matching placebo SC Q4W and diclofenac 75 mg oral, twice daily and NSAID matching placebo oral once daily
- Fasinumab-matching placebo SC Q4W, celecoxib 200 mg oral once daily, and NSAID-matching placebo oral once daily
- Fasinumab-matching placebo SC Q4W and NSAID-matching placebo oral, twice daily

Randomization will be stratified according to the affected index joint (hip or knee), the K-L score (2 to 3, or 4) at the screening visit, and geographical region (Asia/Pacific, Europe and North America).

2.2. Sample Size and Power Considerations

Assuming a 2-sided alpha level of 0.05 and a 20% dropout rate up to week 24, an enrollment of 600 patients in the fasinumab 1 mg Q4W group and 300 patients in the placebo group will provide at least 99% power to detect an effect size of 0.46 in the WOMAC pain and physical function subscale scores (i.e., absolute treatment difference of 1.1 between fasinumab and placebo with a SD of 2.4). The assumed treatment difference and standard deviation (SD) are based on results from study R475-PN-1227. The sample size will provide 99% power to detect

an effect size of 0.36 in PGA (i.e., absolute treatment difference of 0.4 with a SD of 1.1, R475-PN-1227).

Assuming a 2-sided alpha level 0.05 and a 20% dropout rate up to week 24, an enrollment of 600 patients in the fasinumab 1 mg Q4W group and the pooled NSAIDs group will provide approximately 92% power to detect an effect size of 0.22 in the WOMAC pain subscale (i.e., absolute treatment difference of 0.51 with a SD of 2.3, [Schnitzer 2015]). The sample size will provide 95% power to detect an effect size of 0.24 in WOMAC physical function subscale (i.e., absolute treatment difference of 0.50 with a SD of 2.1, [Schnitzer 2015]), and 79% power to detect an effect size of 0.18 in PGA (i.e., absolute treatment difference of 0.18 with a SD of 1.0 [Ekman 2014]).

The sample size has been revised from 2700 patients in the previous amendments to approximately 1620 patients in amendment 4 due to the discontinuation of fasinumab 3 mg Q4W and 6 mg Q8W dose regimens. There will be approximately 600 patients randomized to the fasinumab 1 mg SC Q4W group, 300 patients randomized to the each of the NSAID groups, and 300 patients randomized to the placebo group (a total of 1500 patients). In addition, approximately 60 patients each were enrolled in the fasinumab 3 mg SC Q4W and 6 mg SC Q8W groups under earlier versions of the protocol before dosing was discontinued in these treatment groups.

2.3. Study Plan

Study assessments and procedures are presented by study period and visit in Section 10.2, Table 2.

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 populations of analysis will be used for all statistical analysis:

3.1. The Full Analysis Set (FAS)

The full analysis set (FAS) includes all randomized patients excluding patients affected by the urgent safety measure (i.e. patients randomized to the 3 mg Q4W or 6 mg Q8W doses) and is based on the treatment allocated (as randomized). Efficacy endpoints will be analyzed using the FAS including patients randomized to fasinumab 1 mg Q4W, NSAIDs, and placebo.

Efficacy data from patients randomized to fasinumab 3 mg Q4W or 6 mg Q8W will not be included in the analysis, but will be summarized descriptively in separate tables.

3.2. The Modified Full Analysis Set (FAS)

The modified full analysis set (mFAS) includes all randomized patients in the FAS but excludes patients from four sites ([redacted]) for which there were potential concerns regarding data quality. The co-primary endpoints and selected secondary endpoints may be evaluated in the mFAS as a sensitivity analysis.

3.3. The Per Protocol Set (PPS)

The per protocol set (PPS) will include all randomized patients from the FAS who complete the 24-week treatment period and who do not have to be excluded due to relevant protocol deviations. The PPS will be used to perform sensitivity analyses for the primary and selected secondary endpoints.

Section 10.4 contains the list of protocol violations which lead to exclusion from the PPS and corresponding PDID.

3.4. The Safety Analysis Set (SAF)

The safety analysis set (SAF) includes all randomized patients from the FAS 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 including patients randomized to fasinumab 1 mg Q4W, NSAIDs, and placebo.

Determination of ‘as-treated’ will be performed in the following stepwise manner:

- If a patient receives at least one dose of fasinumab, ‘as treated’ implies the patients data will be analyzed under the fasinumab arm.
- If a patient receives no doses of fasinumab and was ever dispensed NSAIDs, ‘as treated’ implies the patients’ data will be analyzed under the NSAID arm.
- If a patient receives no doses of either fasinumab or NSAID, the patients data will be analyzed under the placebo arm.

Safety data from patients randomized to fasinumab 3 mg Q4W or 6 mg Q8W will not be included in the main safety analysis summaries, but will be summarized in separate tables.

3.5. The Urgent Safety Measure Set (USMS)

The USMS will include all patients randomized to fasinumab 3 mg Q4W or 6 mg Q8W and is based on the treatment allocated (as randomized). The USMS will be utilized for all analyses of data collected from its included patients.

3.6. The Pharmacokinetic (PK) Analysis Set

The PK analysis population includes all treated patients who received any study drug and who had at least 1 non-missing drug concentration result following the first study dose. Patients will be analyzed according to the treatment actually received (as treated).

3.7. The Anti-Drug Antibody Analysis (ADA) Set

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

3.8. The Neutralizing Antibody (Nab) Analysis Set

The neutralizing antibody (NAb) analysis set includes all patients who received any study drug and who are negative in the ADA assay or with at least 1 non-missing result in the NAb assay following first dose of the study drug. Patients who are ADA negative are set to negative in the NAb analysis set. Patients will be analyzed according to the treatment actually received.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic and baseline variables will be summarized:

- Age at screening (year)
- Age group (< 65, 65-74, >=75)
- Sex (Male, Female)
- Race (White, Black/African American, 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
- Geographic Region (North America, Europe, and Asia Pacific/South Africa)
- Index Joint (Knee or Hip) per IWRS
- Kellgren-Lawrence score (2, 3, 4) per IWRS for index joint
- Kellgren-Lawrence 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

4.2. Medical History

Medical history will be recorded at screening and 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 and Concomitant Medications and Procedures

Medications/Procedures will be recorded from the day of informed consent until the end of Follow-up Clinic Visit at Week 44 or the early termination visit.

Medications will be coded to the 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 the On-Treatment Period (as defined in Section 5.8) and ending during or after the On-Treatment Period.

Post-Treatment medications/procedures are medications/procedures starting after the On-Treatment Period.

4.4. Prohibited Medications

Opioid analgesic medications (including tramadol) are prohibited through the week 24 study visit. NSAIDs (oral or topical, except up to 150 mg/day of aspirin/5-ASA, which is permitted for cardiac prophylaxis) are prohibited until at least 16 weeks after the last SC 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
- Anticoagulants and antiplatelets (e.g., warfarin, heparins, factor Xa inhibitors, thrombin inhibitors, aspirin/5-ASA >150 mg daily, clopidogrel)
- 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
- Combination therapy of diuretics with either an ACE inhibitor or ARB

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 Variable

4.5.1. Primary Efficacy Variable(s)

The co-primary endpoint in the study are:

1. Change in the WOMAC pain subscale scores from baseline to week 24 in patients treated with fasinumab compared to patients treated with placebo.
2. Change in the WOMAC physical function subscale scores from baseline to week 24 in patients treated with fasinumab compared to patients treated with placebo.

4.5.2. Secondary Efficacy Variable(s)

The key secondary endpoints in the study are:

1. Change from baseline to week 24 in Patient Global Assessment (PGA) in patients treated with fasinumab compared to patients treated with placebo
2. Percentage of patients treated with fasinumab, compared to patients treated with placebo, who had a response at week 24, with response defined as an improvement by ≥30% in WOMAC pain sub scale score
3. Change from baseline to week 24 in WOMAC pain subscale scores in patients treated with fasinumab compared to patients treated with NSAIDs (pooled celecoxib and diclofenac arms)
4. Change from baseline to week 24 in WOMAC physical function subscale scores in patients treated with fasinumab compared to patients treated with NSAIDs (pooled celecoxib and diclofenac arms)
5. Change from baseline to week 24 in PGA score in patients treated with fasinumab compared to patients treated with NSAIDs (pooled celecoxib and diclofenac arms)

4.5.3. Exploratory Variable(s)

The exploratory endpoints in the study are

- Change from baseline to week 24 in patient-reported outcome measures in patients with pain due to OA of the knee or hip treated for up to 24 weeks with fasinumab compared to placebo
- Change from baseline to week 24 in patient-reported outcome measures in patients with pain due to OA of the knee or hip treated for up to 24 weeks with fasinumab compared to NSAIDs (pooled celecoxib and diclofenac arms)

- The proportion of patients taking rescue medication, number of days on rescue medication, and weekly average use of rescue medication from baseline to week 24 in patients with pain due to OA of the knee or hip treated for up to 24 weeks with fasinumab compared to placebo
- The proportion of patients taking rescue medication, number of days on rescue medication, and weekly average use of rescue medication from baseline to week 24 in patients with pain due to OA of the knee or hip treated for up to 24 weeks with fasinumab compared to NSAIDs (pooled celecoxib and diclofenac arms)
- Change in WOMAC pain subscale scores from baseline to the average score across Weeks 12, 16, 20 and 24 with fasinumab compared to placebo
- Change in WOMAC physical function subscale from baseline to the average score across Weeks 12, 16, 20 and 24 with fasinumab compared to placebo

4.6. Safety Variables

Patient safety will be assessed through the collection of reported adverse events (AEs), clinical laboratory data, vital signs, electrocardiogram (ECG), survey of autonomic symptoms questionnaire, neurological and physical examinations and imaging. Unless otherwise noted, the baseline value is defined as the last available value before the first administration of study drug.

4.6.1. Adverse Events and Serious Adverse Events

Adverse events and serious adverse events will be collected from the time of informed consent signature and until the end of the follow-up period (week 44). All adverse events are to be coded to a "Preferred Term (PT)" and associated primary "System Organ Class (SOC)" according to the Medical Dictionary for Regulatory Activities (MedDRA, the latest current available version).

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

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

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.

4.6.2. 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.

4.6.3. 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 10.2).

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 10.3 for PCSV definitions).

4.6.4. Vital Signs

The following vital signs parameters will be collected according to the Schedule of Events in Section 10.2:

- Body temperature (^{o}C)
- 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. Potentially clinically significant values (PCSV) ranges will be applied to the vital sign parameter values as applicable (see Appendix 10.3 for PCSV definitions).

4.6.5. Orthostatic Hypotension

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

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

  OR

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

  OR

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

  OR

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

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

4.6.6. 12-Lead Electrocardiography (ECG)

A standard 12-lead ECG will be performed according to the Schedule of Events in Appendix 10.2. Heart rate will be recorded from the ventricular rate and the PR, QRS, and QT, QTc intervals, and ECG status (normal, abnormal not clinical significant or abnormal clinical significant) will also be recorded.

QTcF and QTcB are defined as follows:

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

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

Potentially clinically significant values (PCSV) ranges will be applied to the ECG parameter values as applicable (see Appendix 10.3 for PCSV definitions).

4.6.7. 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 10.2.

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 domain 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.

4.6.8. 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:
  - The Joint Pain Questionnaire serves as a monitoring tool that prompts further evaluations of joints, as deemed necessary by the investigator.
  - Summaries will include :
    - Number of subjects with significantly worse joint pain in any joint at each scheduled visit
    - Number of subjects with significantly worse joint pain by joint at each scheduled visit
- Joint space width for the index joints as well as other knee or hip joints at each scheduled visit (taken from bilateral x-rays)
- All-cause Joint replacements:
  - Number and percentage of patients with joint replacement (all-cause joint replacements)
  - Reason for joint replacement (all cause joint replacements)
  - Time to joint replacement (all cause Joint replacements)
- 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 pharmacokinetic variable is the concentration of fasinumab in serum at the time points specified in Table 1 of the protocol.

4.8. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, NAb status, at each time-point/visit. Serum samples for ADA will be collected at the clinic visits specified in Appendix 10.2.

4.9. Quality-of-Life Variables

The following patient reported quality-of-life outcome measures will be summarized:

- Change from baseline by visit in the SF-36 subscale scores including physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health, physical component score, and mental component score
- Change from baseline by visit in the EQ-5D-5L VAS and utility index scores. The EQ-5D-5L utility index will be calculated using UK time-trade-off value set which maps each health state to an index score that quantify health status
- Change from baseline by visit in the TSQM domain scores including effectiveness, side effects, convenience and global satisfaction score

4.10. Health Economic Variables

The following patient reported health economic outcome measures will be summarized:

- HealthCare Resource Utilization (HCRU) including total and type of usage and hospitalizations
- Change from baseline by visit in the WPAI-OA item and sub scores including absenteeism, presenteeism, work productivity loss and activity impairment

5. STATISTICAL METHODS

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

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 44 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 the FAS.

5.2. Medical History

All reported patient's medical history and surgical history will be presented showing patient counts (percentages) by primary SOC and PT by treatment group and overall for the study based on the SAF. The tables will be sorted by decreasing frequency of primary SOC in the overall group. Within each primary SOC, PTs will be sorted by decreasing frequency in the overall group.

5.3. Prior/Concomitant Medications

Summaries will present patient counts (and percentages) for all medications, dictionary coded by WHO, by decreasing frequency of the overall group incidence (or fasinumab 1mg Q4W group incidence in tables where the overall is not presented) of ATC followed by ATC level 2, ATC level 4 and preferred term. In case of equal frequency across anatomic or therapeutic categories, alphabetical order will be used. Patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication, but may be counted several times for the same medication.

The following will be summarized:

- All prior medications will be summarized by treatment group and overall, based on the SAF.
- All concomitant medications taken during the On-Treatment Period will be summarized by treatment group based on the SAF.

- All Post-treatment medications taken during the Post-Treatment period will be summarized by treatment group based on the subset of patients in the SAF.

5.4. Prohibited Medications

Prohibited Medications

Summaries of prohibited medications will present patient counts (and percentages) for all prohibited medications, dictionary coded by WHO, by decreasing frequency of the overall group incidence (or fasinumab 1mg Q4W group incidence in tables where the overall is not presented) of ATC followed by ATC level 2, ATC level 4 and preferred term. In case of equal frequency across anatomic or therapeutic categories, alphabetical order will be used. Patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication, but may be counted several times for the same medication.

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

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

5.5. Subject Disposition

The disposition of patients in the study will be summarized by treatment group and overall based on the FAS.

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

5.6.1. Measurement of Compliance

SC Study Drug Injection

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 treatment compliance to the SC study drug injection will be summarized by treatment groups via descriptive statistics based on the SAF.

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.

Oral NSAID Study Drug

Overall treatment compliance to oral NSAID study drug is defined as the total oral dose actually taken divided by the expected total oral dose of treatment during the treatment exposure period up to patient discontinuation from the treatment phase. It is calculated according to the following formula based on the NSAID/Placebo Dispensing/Accountability eCRF:

$$\frac{\sum_{all\ treatment\ visits(}Number\ of\ pills\ dispensed - Number\ of\ pills\ returned)}{(date\ of\ last\ dose\ of\ oral\ study\ drug - date\ of\ first\ dose\ of\ oral\ study\ drug + 1) * 2}\ x\ 100$$

Overall treatment compliance to oral study drug during the On-Treatment Period will be summarized descriptively by treatment group based on the SAF.

5.6.2. Exposure to Study Drugs

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

= (Date of last SC injection of study drug in the on-treatment period – date of the first SC injection of study drug administration in the on-treatment period) + 28

The duration of treatment exposure to oral study drug will be calculated as:

= (Date of last dose of oral study drug in the on-treatment period – date of first dose of oral study drug in the on-treatment period) + 1

The duration of exposure will be summarized by treatment group using descriptive statistics based on the SAF.

The number and percentage of patients exposed to study drug will be presented by specific time period for each treatment group based on the SAF. The time periods of interest are specified as: ≥ 1 day, ≥ 29 days, ≥ 57 days, ≥ 85 days, ≥ 113 days, ≥ 141 days, ≥ 169 days.

5.6.3. Length of Study Observation

The length of study observation will be calculated as:

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

The length of total study participation will be calculated as:

= (Date of the last study visit[up to the End of study phone call] – date of the first study drug administration) + 1

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

The number and percentage of patients with observation and participation periods will be presented by treatment group based on the SAF. The time periods of interest are specified as: ≥ 1 day, ≥ 29 days, ≥ 57 days, ≥ 85 days, ≥ 113 days, ≥ 141 days, ≥ 169 days, ≥ 197 days, ≥ 225 days, ≥ 253 days, ≥ 281 days, ≥ 309 days).

5.7. Analyses of Efficacy Variables

Unless stated otherwise, all efficacy analyses will be based on the FAS. Confidence intervals will be constructed with level of confidence equal to 95%. With the exception of analyses based on the PPS, models including stratifying variables will utilize the value of these variables as captured in the IWRS system.

5.7.1. Analysis of Primary Efficacy Variable(s)

The co-primary efficacy variables are:

1. Change in the WOMAC pain subscale scores from baseline to week 24
2. Change in the WOMAC physical function subscale score from baseline to week 24

The following hypotheses will be tested:

- H_1: There is no treatment difference between fasinumab 1 mg Q4W and placebo in WOMAC pain or physical function subscale at week 24 versus there is treatment difference in WOMAC pain and physical function subscale score at week 24

For H_1, the estimand is the difference in means between the fasinumab 1 mg Q4W dose+ protocol-defined rescue medication and placebo+ protocol-defined rescue medication in the change from baseline to week 24 in the WOMAC pain and physical function scores in the FAS, regardless of whether or not rescue medication or prohibited medication had been taken. Any data collected after discontinuing treatment will not be used in the primary efficacy analysis, but used in a treatment policy sensitivity analysis.

The co-primary efficacy variables will be analyzed separately using a multiple imputation approach with a mixed-effect model for repeated measures (MMRM) based on the FAS. For patients who discontinued treatment due to lack of efficacy or AEs or deaths, 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 the patient was randomized to. For patients who discontinued treatment due to other reasons including discontinuation because of public health measures implemented in response to COVID-19, their missing WOMAC subscale scores after discontinuation will be imputed under the 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], index joint [knee, hip], and geographical region [Other, Europe, North America]) and baseline WOMAC subscale score. Intermittently missing WOMAC subscale scores prior to treatment discontinuation will be imputed using the Markov Chain Monte Carlo method.

Missing data up to week 24 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 4751688. Any score imputed outside the range of the WOMAC subscale score of 0-10 will be truncated to the nearest permissible value on the WOMAC scale according to the following algorithm:
  - If the imputed score > 10, then the final imputed score will be 10.
  - If the imputed score < 0, then the final imputed score will be 0.
- 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 4751688 and adjustment for covariates including treatment groups, randomization strata (K-L category [2 to 3, or 4], index joint [knee, hip], and

geographical region [Other, Europe, North America]), baseline WOMAC subscale score and all WOMAC subscale scores at preceding visits. Scores that are imputed outside the range of the WOMAC subscale will be truncated in the same manner as in step 1. As the regression method imputes missing data sequentially by visits, the truncation will be implemented after each visit iteration.

- Step 3: For patients who permanently discontinued study treatment due to lack of efficacy, death 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., imputed score =initial 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). Scores that are adjusted to outside the range of the WOMAC subscale will be truncated in the same manner as in step 1.

Each imputed data set will be analyzed using a MMRM with terms for baseline WOMAC subscale score, randomization strata (K-L category [2 to 3, or 4], index joint [knee, hip], and geographical region [Other, Europe, North America]), treatment, visit, and treatment-by-visit interaction. 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 fit 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 24, as well as the difference of these 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 hypothesis for H_1, will be rejected when the p-values corresponding to the difference in change from baseline to week 24 between fasinumab 1 mg Q4W and placebo is less than the available α_0 (see Section 5.7.4) for both the WOMAC pain subscale score and physical function subscale score.

Sensitivity analysis:

Three sensitivity analyses will be performed to assess the robustness of the results generated for the primary efficacy analysis.

Analysis of Treatment Policy Estimand

Sensitivity analysis of the treatment policy estimand for the co-primary endpoints will be performed using similar analysis methods as the primary efficacy analysis. The treatment policy estimand is the difference in means between each fasinumab dose+ protocol-defined rescue medication and placebo+ protocol-defined rescue medication in the change from baseline to week 24 in the WOMAC pain and physical function scores based on the FAS, regardless of study treatment discontinuation prior to week 24 and regardless of whether or not rescue medication or prohibited medication had been taken. Hence, data from all patients, including

data collected after discontinuing treatment up to week 24 will be used in this sensitivity analyses. Missing WOMAC subscale scores up to week 24 will be imputed using the same approach as in Section 5.7.1.

Tipping Point Analysis

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

This approach will introduce a sensitivity parameter, δ. Estimations will be performed using multiple imputation methodology. Missing data up to week 24 timepoint will be imputed 50 times to generate 50 complete datasets by using SAS procedure PROC MI for each δ following the 2 steps below:

- Step 1: The monotone missing pattern is induced by Markov Chain Monte Carlo (MCMC) method in MI procedure using seed number 4751688. Any score imputed outside the range of the WOMAC subscale score of 0-10 will be truncated to the nearest permissible value on the WOMAC scale according to the following algorithm:
  - If the imputed score > 10, then the final imputed score will be 10.
  - If the imputed score < 0, then the final imputed score will be 0.
- 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 4751688 and adjustment for covariates including treatment groups, randomization strata (K-L category [2 to 3, or 4], index joint [knee, hip], and geographical region [Other, Europe, North America]), baseline WOMAC subscale score and all WOMAC subscale scores at preceding visits. Scores that are imputed outside the range of the WOMAC subscale will be truncated in the same manner as in step 1. As the regression method imputes missing data sequentially by visits, the truncation will be implemented after each visit iteration.
- Step 3: For missing data because of permanent study treatment discontinuation due to adverse events, deaths or lack of efficacy, δ will be added to the imputed values (δ = 0 corresponds to the MAR assumption). Scores that are adjusted to outside the range of the WOMAC subscale will be truncated in the same manner as in step 1.

Each imputed data set will be analyzed using a MMRM model with terms for baseline WOMAC subscale score corresponding to the efficacy variable being analyzed, randomization strata (K-L category [2 to 3, or 4], index joint [knee, hip], and geographical region [Other, Europe, North America]), treatment, visit, and treatment-by-visit interaction. For each δ the SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 50 analyses using Rubin's formula. By progressively increasing δ, the sensitivity analysis will explore the tipping points, e.g., δ value when the p-value for a treatment comparison is above 0.05. Results will be then summarized using summary tables and graphs.

Per Protocol Set Analysis

Sensitivity analyses based on the PPS will be performed using the same approach as specified for the primary analysis in the beginning of this section. Values of the stratifying variables utilized for analysis on the PPS will be those captured in the EDC system.

USM Analysis Set

WOMAC Pain and Physical function will be summarized descriptively based on the USM Analysis set. No sensitivity analysis will be conducted using the USM analysis set.

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]
- Region [North America, Europe, Other]
- Age group [< 65, 65-74, >=75]
- Sex [Male, Female]
- Weight group [< Median, ≥ Median]
- BMI group [≤ Median, > Median]
- Flare status [Flare, non-flare] : Flare patients are defined as patients who experience a ≥ 1 point increase in WOMAC pain scores from the Screening to the Baseline Visit

An MMRM model analogous to that used for the primary analysis will be constructed, also including terms for subgroup and subgroup-by-treatment, subgroup-by-visit and subgroup-by treatment-by visit interactions as fixed effects. Multiple imputation will not be performed for the subgroup analyses. In addition to the actual change from baseline values, their LS means, differences of LS Means between treatment groups and corresponding 95% CIs within each subgroup at each visit will be presented. The p-value corresponding to the overall effect of the overall subgroup-by-treatment interaction will be supplied. Forest plots for the subgroup analysis will be provided.

5.7.3. Analysis of Secondary Efficacy Variables

The following secondary hypotheses specified in the study protocol that will be tested:

- H_2: There is no treatment difference between fasinumab 1 mg Q4W and placebo in the Patient Global Assessment score at week 24 versus there is treatment difference in Patient Global Assessment score at week 24
- H_3: There is no treatment difference between fasinumab 1 mg Q4W and placebo in the proportion of patients with ≥30% improvement in the WOMAC pain subscale

scores at week 24 versus there is treatment difference in proportion of patients with ≥30% improvement in WOMAC pain at week 24

- H_4: There is no treatment difference between fasinumab 1 mg Q4W and NSAIDs in the WOMAC pain subscale scores at week 24 versus there is treatment difference in WOMAC pain subscale scores at week 24
- H_5: There is no treatment difference between fasinumab 1 mg Q4W and NSAIDs in the WOMAC physical function subscale scores at week 24 versus there is treatment difference in WOMAC physical function subscale scores at week 24
- H_6: There is no treatment difference between fasinumab 1 mg Q4W and NSAIDs in the Patient Global Assessment score at week 24 versus there is treatment difference in Patient Global Assessment score at week 24

The hypotheses H_4 and H_5 can be tested within the same analysis method used to test H_1 as described in Section 5.7.1.

To test H_2 and H_6, a method analogous to that used to test H_1 in Section 5.7.1 can be utilized, replacing the respective WOMAC subscale score with the PGA score. The multiple imputation algorithm will be modified to truncate values outside the range of the PGA score (0-5) in a manner similar to the primary analysis.

To test H_3 the Cochran Mantel Haenszel (CMH) approach stratified by the randomization strata (K-L category [2 to 3, or 4], index joint [knee, hip], and geographical region[Other, Europe, North America]) will be used with missing data considered as non-response.

5.7.4. Adjustment for Multiple Comparison

To control the overall Type I Error of the clinical trial at 5%, the sequentially rejective multiple test procedure (Bretz 2009) will be applied. Hypothesis H_1 will be tested at $\alpha_0 = 0.05$. As it is a hypothesis test concerning the co-primary endpoints, the hypothesis will be rejected if the following is met:

- The hypothesis of no treatment difference between fasinumab 1 mg Q4W and placebo in WOMAC pain subscale at week 24 is rejected $\alpha_0 = 0.05$

  AND

- The hypothesis of no treatment difference between fasinumab 1 mg Q4W and placebo in WOMAC physical function subscale at week 24 between fasinumab and placebo is rejected $\alpha_0 = 0.05$

If a hypothesis is rejected, the alpha level for that hypothesis will be reallocated to other hypothesis according to the graph. The graph will be updated according to the pre-specified algorithm, as described by Bretz 2009. The rest of the hypotheses will be tested at the updated alpha level based on the updated graph. The testing will stop when no hypothesis can be rejected at any step.

If the primary analysis of efficacy is successful, secondary endpoints will be tested according to hierarchical testing strategy based on the following order:

$H_3 \rightarrow H_2 \rightarrow H_4 \rightarrow H_5 \rightarrow H_6$

5.7.5. Analysis of Other Efficacy Variables

Responder Analysis

The percentage of patients who are responders based on WOMAC pain and physical function subscale scores defined by at least a 30% reduction and at least a 50%, 70% reduction from baseline to each post-baseline week will be summarized and plotted by treatment group. The percentage of patients who are responders based on the Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criterial Initiative and THE Outcome Measure in Rheumatology (OMERACT -OARSI) responder criteria will be summarized and plotted by treatment group. Cochran -Mantel-Haenszel (CMH) test, stratified by the randomization strata will be applied for the responder analysis. Missing data is considered as non-response in this analysis.

Cumulative distribution of percent change from baseline to Week 24 in the WOMAC pain and physical function 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 distribution curve.

Walking Index Joint Pain Numeric Rating Score (NRS)

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

The MMRM model will include the randomization strata (K-L category [2-3 vs. 4], index joint [hip or knee] and geographic region), treatment, week (weeks 1, 2, …, 24), treatment-by-week interaction as fixed effects, and baseline average NRS value as a covariate. The least-squares (LS) means for the mean change from baseline to each week, as well as the LS mean differences between fasinumab doses and placebo, with their corresponding standard errors (SEs), p-values and associated 95% confidence intervals, will be provided from the MMRM. If the model does not converge using unstructured covariance matrix, an autoregressive 1 covariance structure will be used.

Rescue Medications

The number (and percentage) of patients using rescue medication, during the Pre-Treatment Period will be summarized by treatment group and overall based on the SAF. Similar analysis will be performed for the On-Treatment Period based on the SAF.

For patients taking rescue medication, descriptive statistics of the number of days patients took rescue medications will be presented by treatment group during the On-Treatment Period based on the SAF.

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

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

Descriptive statistics of the weekly average usage of rescue medications for OA pain will be presented by treatment group based on the SAF.

Averagev WOMAC pain ann physical function Score across Week 12 to Week 24

Change in WOMAC pain and physical function subscale scores from baseline to the average score across Weeks 12, 16, 20 and 24 will be analyzed using the same multiple imputation method used to analyze the primary efficacy endpoints in Section 5.7.1. However, the analysis model for the average of the WOMAC subscale scores across multiple visits will instead be an ANCOVA model with terms for baseline WOMAC subscale score, randomization strata (K-L category [2 to 3, or 4], index joint [knee, hip], and geographical region [Europe, North America, Other]) and treatment.

5.7.6. Analysis of Quality-of-Life and Health Economic Variables

The following patient reported outcomes will be summarized and analyzed. Analysis results for exploratory objectives will be included in the final CSR.

EuroQol 5 Dimensions 5 Level Questionnaire (EQ-5D-5L)

The health states defined by the 5-dimensional classification will be converted into the corresponding index score. The EQ-5D-5L index will be set to missing if any of the 5 dimensions is missing.

An MMRM model will be fit to the EQ-5D-5L Visual Analog Scale and index scores include the randomization strata (K-L category [2-3 vs. 4], index joint [hip or knee] and geographic region), treatment, visit, treatment-by-visit interaction as fixed effects, and baseline value as a covariate. The least-squares (LS) means for the mean change from baseline to each visit, as well as the LS mean differences between fasinumab and placebo and NSAID groups, with their corresponding standard errors (SEs), p-values and associated 95% confidence intervals, will be provided from the MMRM.

36-Item Short Form Medical Outcome Study Questionnaire, Version 2 (SF-36)

The same analysis used for the EQ-5D-5L will be performed for the subscale scores of the SF-36 using analogous MMRM models. SF-36 subscale scores will be computed if at least 50% of component items are available. The missing items will be imputed by the mean of available items.

Health Care Resource Utilization Questionnaire (HCRU)

The utilization of each resource captured on the HCRU will be summarized via descriptive statistics by treatment group for each visit.

Work Productivity and Activity Impairment-Osteoarthritis (WPAI-OA)

The number and percentage of patients who reported they were working/non-working on Question 1 of the WPAI-OA will be presented by treatment group for each visit. Furthermore, for patients who answered ‘YES’ to Question 1 at that visit, the absenteeism, presenteeism, work productivity loss and activity impairment scores will also be constructed. The same analysis used for the EQ-5D-5L will be presented for all four scores of the WPAI-OA using analogous MMRM models.

Treatment Satisfaction Questionnaire for Medicine (TSQM)

The same analysis used for the EQ-5D-5L will be performed for the effectiveness, side effects, convenience and global satisfaction domain scores of the TSQM using analogous MMRM models. The missing items will be imputed by the mean of available items.

5.8. Analysis of Safety Data

The analysis of safety and tolerance will be performed on the SAF, as defined in Section 3.4.

The safety analysis will be based on the reported AEs and other safety information (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 investigational product, Day –1 is the day before; there is no Day 0.

The time interval to detect any AEs, including AESIs (except JR identified at the 72-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 44/Early Termination). Any study drug-related SAEs occurring between the end of Follow-Up clinic visit and the End of Study 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. Adverse Events

The verbatim text, the preferred term (PT), and the primary system organ class (SOC) will be displayed in subject listings. Summaries that include frequencies and proportions of patients reporting AEs will include the PTs and the SOCs.

For details on handling missing data and partial dates, see Section 6.3.

Summaries of AE incidence 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
  - Total number of serious AESIs
  - Patients with any TEAEs
  - Patients with any serious TEAEs

  - Patients with any AESI's
  - Patients with any serious AESIs
  - Patients with any TEAEs leading to permanent study treatment discontinuation
  - Patients with any TEAEs leading to withdrawal from study
  - Patients with any TEAEs leading to death
- TEAEs by SOC and PT
  - All TEAEs
  - TEAEs by severity: mild, moderate or severe
  - TEAEs resulting in permanent study treatment discontinuation
- Study drug-related TEAEs by SOC and PT
  - All TEAEs
  - TEAEs by severity: mild, moderate or severe
  - TEAEs resulting in permanent study treatment discontinuation
- 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
  - All serious TEAEs
- Post-treatment Serious AEs by SOC and PT
- All serious AEs on study by SOC and PT
- Non - Serious TEAEs by SOC and PT
  - All non-serious TEAEs
- 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
- Deaths

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 descending frequency of the 'Fasinumab 1 mg SC Q4W' treatment group. Within each primary SOC, PTs will be sorted by decreasing frequency of investigational product.

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 treatment (not applicable to post-treatment AEs)
- TEAEs leading to withdrawal from study
- Patients with Serious TEAEs
- AESIs by AESI type
- Deaths
- All Joint Replacements
- Pre-treatment AEs
- Post-treatment AEs

5.8.2. Analysis of Adverse Events of Special Interest

Adverse events of special interest (AESI) include adjudicated arthropathies, AEs confirmed as SNS dysfunction and 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

5.8.3. 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 Potential Clinically Significant abnormal value (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. Definitions of PCSV is listed in Section 10.3. Treatment-Emergent Potentially clinically significant values (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. 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 other AA subtype except RPOA-1)
- 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 Period. Lab data collected during the Pre-Treatment and Post-Treatment Periods will be displayed in listings.

5.8.4. Analysis of Vital Signs

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

A treatment-emergent Potential Clinically Significant abnormal value (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 Potentially clinically significant values (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.

5.8.5. Analysis of 12-Lead ECG

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 by treatment group.

A treatment-emergent Potential Clinically Significant abnormal value (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 Potentially clinically significant values (PCSVs) will be summarized by treatment group.

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

5.8.6. 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.

5.8.7. Analysis of Other Safety Variables

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

Adjudicated Arthropathry

Adjudicated arthropathy events based on imaging data overall and by subtype will be summarized by treatment group based on the SAF. Time to first AA event will be summarized by Kaplan-Meier method. 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.

Time to first DA event will be summarized by Kaplan-Meier method. 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

Plots of the Kaplan Meier curves by treatment group (as randomized) of time to JR will be presented based on the SAF, regardless of what period in the study the JR occurred. Patients without an event will be censored at the last contact.

Data from Urgent Safety Measure Patients

Limited safety summaries will be presented based on the USM Analysis set including TEAEs and summaries of AAs, DAs and all joint replacements.

5.9. Analysis of Pharmacokinetic Data

Summaries of fasinumab concentrations in serum will be presented by nominal time point. Individual patient concentration data will be plotted by actual time. Plots of mean and median serum concentrations of fasinumab will be presented by nominal time.

Correlation analyses of fasinumab concentrations in serum vs efficacy and safety endpoints may be performed, as appropriate.

5.10. Analysis of Immunogenicity Data

5.10.1. Analysis of ADA Data

The immunogenicity variables described in Section 4.7 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:

- 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 subjects/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. Analysis of Neutralizing Antibody (NAb) Data

The absolute occurrence (n) and percent of patients (%) with NAb status in the NAb analysis set will be provided by treatment groups.

5.10.3. Association of Immunogenicity with Exposure, Safety and Efficacy

5.10.3.1. 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 periodInjection site reaction (serious or severe and lasting 24 hours or longer)

- Hypersensitivity (SMQ: Hypersensitivity [Narrow])
- Anaphylaxis (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 safety and efficacy analyses mentioned above 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.
- NAb positive patients, that is ADA positive patients who were positive in the NAb assay at any time point analyzed.
- 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.

6.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the baseline value is defined as the last available valid measurement prior to randomization.

6.2. Data Handling Convention for Efficacy Variables

6.2.1. Data Handling Convention for Efficacy Variables due to COVID-19 Pandemic

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 (Bellamy 2002). Sensitivity analysis may be performed excluding data collected via telephone.

6.3. Data Handling Convention for Repeat Measurements

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 assessments 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 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 JPQ.

6.4. Data Handling Convention for Missing Data

Rules for handling missing data for primary and secondary efficacy variables are described in Section 4.5.1 and Section 4.5.2.

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 dates

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 present, missing AE/concomitant medication end day will imputed to the last day of the month.

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

Handling of 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 questionnaires

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.

SF-36

The Half-Scale rule will be used to impute missing item responses in the SF-36 subscale scores i.e. a score will be computed if the respondent answers at least 50% of items in that scale. The missing items in the scale will be imputed by the mean of available items rounded to the nearest whole number.

The bodily pain subscale consists of Q7 and Q8 of the instrument. Since Q7 is based on 6pt Likert score and Q8 is based on a 5pt Likert scale and because mean imputation will be meaningless, the bodily pain subscale score will not be imputed if any of the questions making up the scale is missing.

EQ-5D-5L

Index will be set to missing if any of the 5 dimensions is missing.

Laboratory Safety Variables below LLOQ or above ULOQ

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

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

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

Handling of Potentially Clinically Significant Abnormalities

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

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

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; e.g., 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 case report form (CRF) assessment recorded by the investigator. For assessments without a nominal visit number such as Unscheduled, EOT, EOS assessments, and eCOA assessments, a visit number will be assigned based on the actual visit date using the study day analysis window based on the targeted visit study day in Appendix 10.2 Schedule of Events.

The following visit windows will be used to map the unscheduled visits, early study termination visits and eCOA assessments, based on the study day:

Table 1: Analysis Windows

Visit Number	Visit Name	Targeted Study Days[a]	Analysis Window in Study Days
1	Screen	Day -30 to Day -11	[-30, -11]
2	Pre-randomization	Day -10 to -7	[-10, -1]
3	Baseline	1	1
Phone 1	Week 2	15	[2, 22]
4	Week 4	29	[23, 43]
5	Week 8	57	[44, 71]
6	Week 12	85	[72, 99]
7	Week 16	113	[100, 127]
8	Week 20	141	[128, 155]
9	Week 24	169	[156, 196]
10	Week 28	197	[197, 267]
11	Week 44	309	[268, 407]
Phone 2	Week 72	505	≥ 408

[a] 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. Unscheduled Assessments

The determination of baselines and values at the end of treatment 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 adverse events) will be included in listings, but not summaries except for the endpoint determination. If more than one laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.

6.7. Pooling of Centers for Statistical Analyses

Study centers will be pooled according to their geographic region the statistical analysis. The geographic regions are:

- Europe: Estonia, Germany, Poland, Romania, United Kingdom
- North America: United States, Canada
- Other: South Africa, Australia, New Zealand

6.8. Statistical Technical Issues

Not applicable.

7. INTERIM ANALYSIS

- A **First-Step Analysis** of the data will be conducted when 44 week data are available for all randomized patients. No alpha adjustment is necessary, as the week 24 efficacy analysis will be the final primary analysis for efficacy. The results of this analysis will be used in the filing for the BLA submission.
- **120-Day Safety Update:** The analysis for the 120-Day Safety Update will include additional safety data collected upto to the data cutoff date.

8. SOFTWARE

All analyses will be done using SAS Version 9.4.

9. REFERENCES

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4. Bretz, F., W. Maurer, W. Brannath, and M. Posch. A graphical approach to sequentially rejective multiple test procedures. Stat Med. 2009. 28:586-604.
5. Bellamy, N., J. Campbell, H. Hill, P. Band. A comparative study of telephone versus onsite completion of the WOMAC 3.0 Osteoarthritis Index. J Rheumatol 2002. 29:783–6.

10. APPENDIX

10.1. Summary of Statistical Analyses

Efficacy Analysis:

Endpoint	Analysis Populations	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Primary Endpoint						
Co-primary: - *Change from baseline in the WOMAC pain subscale scores* - *Change from baseline in the WOMAC physical function subscale score*	*FAS, PPS*	*Change from baseline at Week 24 in the WOMAC pain subscale scores* *&* *Change from baseline at Week 24 in the WOMAC physical function subscale scores*	*MMRM with multiple imputation*	*Sensitivity Analyses:* - *Treatment Policy Estimand* - *Tipping Point Analysis* - *Analysis using the PPS*	*Subgroups: K-L Category, Index Joint, Region, Age Group, Sex, Weight, BMI Group.*	*For Non-flare patients -* *Change from baseline at Week 24 in the WOMAC pain subscale scores* *&* *Change from baseline at Week 24 in the WOMAC physical function subscale scores*
Secondary/exploratory Endpoints						
- *Change from baseline in the WOMAC pain subscale scores* - *Change from baseline in the WOMAC physical function subscale score*	*FAS*		*MMRM with multiple imputation*			*Change from baseline at all intermediate visits in WOMAC pain and physical function scores*
- *Change from baseline in WOMAC pain subscale scores averaged across multiple timepoints*	*FAS*	*Change from baseline in WOMAC pain subscale scores averaged across Weeks 12, 16, 20 and 24*	*ANCOVA with multiple imputation*			

Endpoint	Analysis Populations	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
- *Change from baseline in WOMAC physical function subscale scores averaged across multiple timepoints*	*FAS*	*Change from baseline in WOMAC physical function subscale scores averaged across Weeks 12, 16, 20 and 24*	*ANCOVA with multiple imputation*			
Change from baseline in PGA scores	*FAS*	*Change from baseline at Week 24 in the PGA scores*	*MMRM with multiple imputation*		*Subgroups: K-L Category, Index Joint, Region, Age Group, Sex, Weight, BMI Group.*	*Change from baseline at all intermediate visits in PGA scores* *Cumulative distribution frequency plot*
Proportion of patients with ≥ 30% improvement in WOMAC pain subscale	*FAS*	*Proportion of patients with ≥ 30% improvement in WOMAC pain subscale at Week 24*	*CMH Test*	*Sensitivity Analyses:* *- Analysis treating patients who discontinue treatment prior to Week 24 as non-responders*	*Subgroups: K-L Category, Index Joint, Region, Age Group, Sex, Weight, BMI Group.*	*Proportion of patients with ≥ 50 and 70% improvement in WOMAC pain subscale at Week 24*

Safety Analyses:

Endpoint	Analysis Populations	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Treatment Emergent Adverse Events	*SAF*	*Percent of patients by system organ class and preferred term*	*Descriptive Statistics*	*No*	*No*	*Percent of patients by system organ class, preferred term and severity*

Endpoint	Analysis Populations	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Treatment Emergent Serious Adverse Events	*SAF*	*Percent of patients by system organ class and preferred term*	*Descriptive Statistics*	*No*	*No*	*NA*
Treatment-related Treatment Emergent Adverse Events	*SAF*	*Percent of patients by system organ class and preferred term*	*Descriptive Statistics*	*No*	*No*	*Percent of patients by system organ class, preferred term and severity*
Treatment Emergent Adverse Events of Special Interest	*SAF*	*Percent of patients by system organ class and preferred term*	*Descriptive Statistics*	*No*	*No*	*No*
Treatment Emergent Adverse Events Leading to Discontinuation from Study Drug	*SAF*	*Percent of patients by system organ class and preferred term*	*Descriptive Statistics*	*No*	*No*	*NA*
Treatment Emergent Non-Serious Adverse Events	*SAF*	*Percent of patients by system organ class and preferred term*	*Descriptive Statistics*	*No*	*No*	*NA*
Clinical Laboratory Measurements	*SAF*	*Actual and Change from baseline values*	*Descriptive Statistics*	*PCVS Analysis*	*No*	*Shift Table Analysis*
Vital Sign Measurements	*SAF*	*Actual and Change from baseline values*	*Descriptive Statistics*	*PCVS Analysis*	*No*	*Incidence of Orthostatic Hypotension*
12-Lead ECGs	*SAF*	*Actual and Change from baseline values*	*Descriptive Statistics*	*PCVS Analysis*	*No*	*Shift Table Analysis*
Physical & Neurological Exams	*SAF*	*Number of patients with new-onset abnormal examinations findings*	*Descriptive Statistics*	*NA*	*No*	*NA*

Endpoint	Analysis Populations	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Survey of Autonomic Symptoms	*SAF*	*Number of patients reporting the presence of each symptom/health problem*	*Descriptive Statistics*	*Number of Symptoms Reported* *Total Symptom Impact Score*	*No*	*NA*
Adjudicated Arthropathy	*SAF*	*Number of patients requiring adjudication* *Number of patients with adjudicated arthropathy* *Number of patients with destructive arthropathy*	*Descriptive Statistics*	*Time to AA* *Time to DA* *Break-down by subtypes of AA*	*No*	*NA*
Joint Replacements	*SAF*	*Number of patients with joint replacements*	*Descriptive Statistics*	*Time to JR*	*No*	*NA*

10.2. Schedule of Time and Events

Table 2: Schedule of Events

	Screening/ Pre-randomization		Treatment Period									Follow-up Period[1]			EOS
Study Week (wk) Visit (V)/Phone	**Screen V 1**	**Pre-rand V 2**	**Baseline V 3**	**Wk 2 Phone 1**	**Wk 4 V 4**	**Wk 8 V 5**	**Wk 12 V 6**	**Wk 16 V 7**	**Wk 20 V 8**	**EOT Wk 24 V 9**	**ET[1]/ JR Pre-Op Visit**	**Wk 28 V 10**	**Wk 44 V 11**	**ET[1]/ JR Pre-Op Visit**	**Wk 72 Phone 2**
Study Day	Up to 30 Days	7 to 10 Days	1	15	29	57	85	113	141	169		197	309		505
Window (days)				±3	±7	±7	±7	±7	±7	±7		±7	±7		±7
Screening/Baseline:															
Inclusion/ Exclusion[2]	X		X												
Main study Informed Consent	X														
Genomics Sub-study Informed Consent[3]	X														
Medical History	X														
Medication History	X														
Demographics	X														
Height	X														
MRI for index joint, contralateral joint & any hip or knee with K-L ≥3	X														
Instructions for use of diary		X	X												
Training on pain reporting/patient education brochures[4]	X	X													
Randomization			X												

	Screening/ Pre-randomization		Treatment Period									Follow-up Period[1]			EOS
Study Week (wk) Visit (V)/Phone	**Screen V 1**	**Pre-rand V 2**	**Baseline V 3**	**Wk 2 Phone 1**	**Wk 4 V 4**	**Wk 8 V 5**	**Wk 12 V 6**	**Wk 16 V 7**	**Wk 20 V 8**	**EOT Wk 24 V 9**	**ET[1]/ JR Pre-Op Visit**	**Wk 28 V 10**	**Wk 44 V 11**	**ET[1]/ JR Pre-Op Visit**	**Wk 72 Phone 2**
Study Day	Up to 30 Days	7 to 10 Days	1	15	29	57	85	113	141	169		197	309		505
Window (days)				±3	±7	±7	±7	±7	±7	±7		±7	±7		±7
Treatment:															
SC study drug injection[5]			X		X	X	X	X	X						
Dispense oral study drug			X		X	X	X	X	X						
Oral study drug accountability			X		X	X	X	X	X	X	X				
Dispense to home acetaminophen/ paracetamol		X	X		X	X	X	X	X						
Acetaminophen/ paracetamol accountability			X		X	X	X	X	X	X	X				
Record rescue medication use in patient diary[6]		X	X	X	X	X	X	X	X	X	X				
Concomitant therapies (medications and procedures)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Efficacy:															
WOMAC[7]	X		X		X	X	X	X	X	X	X	X	X	X	
PGA	X		X		X	X	X	X	X	X	X	X	X	X	
NRS[8]		X	X		X	X	X	X	X	X	X				
WPAI-OA			X		X	X	X	X	X	X	X				
SF-36			X		X	X		X		X	X		X	X	
EQ-5D-5L			X		X	X	X	X	X	X	X		X	X	

	Screening/ Pre-randomization		Treatment Period									Follow-up Period[1]			EOS
Study Week (wk) Visit (V)/Phone	**Screen V 1**	**Pre-rand V 2**	**Baseline V 3**	**Wk 2 Phone 1**	**Wk 4 V 4**	**Wk 8 V 5**	**Wk 12 V 6**	**Wk 16 V 7**	**Wk 20 V 8**	**EOT Wk 24 V 9**	**ET[1]/ JR Pre-Op Visit**	**Wk 28 V 10**	**Wk 44 V 11**	**ET[1]/ JR Pre-Op Visit**	**Wk 72 Phone 2**
Study Day	Up to 30 Days	7 to 10 Days	1	15	29	57	85	113	141	169		197	309		505
Window (days)				±3	±7	±7	±7	±7	±7	±7		±7	±7		±7
Central vs. peripheral pain Questionnaire			X												
HCRU	X						X			X	X				
TSQM	X				X	X		X		X	X				
Safety:															
Weight	X									X	X		X	X	
Vital Signs[9]	X		X		X	X	X	X	X	X	X	X	X	X	
Physical Examination	X									X	X		X	X	
Orthostatic blood pressure and heart rate assessment[9,10]	X	X	X		X	X	X	X	X	X	X	X	X	X	
Joint pain questionnaire	X		X		X	X	X	X	X	X	X	X	X	X	
Survey of Autonomic Symptoms	X		X		X	X	X	X	X	X	X	X	X	X	
Neurologic examination	X Full		X Brief		X Brief	X Brief	X Brief	X Brief	X Brief	X Full	X Full	X Brief	X Full	X Full	
Adverse events	---------->														
Injection site evaluation			X		X	X	X	X	X						
Bilateral X-rays (knee, hip, shoulder)	X[11]							X		X	X		X	X	
Event-triggered imaging[12]				X	X	X	X	X	X	X	X	X	X	X	

	Screening/ Pre-randomization		Treatment Period									Follow-up Period[1]			EOS
Study Week (wk) Visit (V)/Phone	**Screen V 1**	**Pre-rand V 2**	**Baseline V 3**	**Wk 2 Phone 1**	**Wk 4 V 4**	**Wk 8 V 5**	**Wk 12 V 6**	**Wk 16 V 7**	**Wk 20 V 8**	**EOT Wk 24 V 9**	**ET[1]/ JR Pre-Op Visit**	**Wk 28 V 10**	**Wk 44 V 11**	**ET[1]/ JR Pre-Op Visit**	**Wk 72 Phone 2**
Study Day	Up to 30 Days	7 to 10 Days	1	15	29	57	85	113	141	169		197	309		505
Window (days)				±3	±7	±7	±7	±7	±7	±7		±7	±7		±7
Pre-op questionnaire (JR follow-up)[13]											X			X	
Electrocardiogram	X									X	X				
EOS phone contact[14]															X
MRI of affected joint(s) for AA patients only[15]															X
Laboratory Testing:															
Hematology[16]	X				X			X		X	X		X	X	
Blood Chemistry[16]	X				X			X		X	X		X	X	
ESR	X														
Hb1AC[16]	X														
FSH and estradiol[16,17]	X														
Pregnancy Test (WOCBP)[18]	X Serum		X Urine		X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	
Urinalysis and urine electrolytes[16]	X				X			X		X	X		X	X	
Urine drug test	X														
PK ADA and Research Samples:															
ADA sample[19]			X					X		X	X		X	X	
PK sample[19]			X		X	X		X		X	X		X	X	
hs-CRP sample[19,20]			X		X			X		X	X		X	X	
Research serum/plasma sample[19, 20]			X		X	X		X		X	X		X	X	

	Screening/ Pre-randomization		Treatment Period									Follow-up Period[1]			EOS
Study Week (wk) Visit (V)/Phone	**Screen V 1**	**Pre-rand V 2**	**Baseline V 3**	**Wk 2 Phone 1**	**Wk 4 V 4**	**Wk 8 V 5**	**Wk 12 V 6**	**Wk 16 V 7**	**Wk 20 V 8**	**EOT Wk 24 V 9**	**ET[1]/ JR Pre-Op Visit**	**Wk 28 V 10**	**Wk 44 V 11**	**ET[1]/ JR Pre-Op Visit**	**Wk 72 Phone 2**
Study Day	Up to 30 Days	7 to 10 Days	1	15	29	57	85	113	141	169		197	309		505
Window (days)				±3	±7	±7	±7	±7	±7	±7		±7	±7		±7
Genomic sub-study sample (optional)[3]			X												

AA: Adjudicated arthropathy
ADA: Anti-drug antibody
EOS: End of study
EOT: End of treatment
EQ-5D-5L: EuroQoL 5 Dimensions 5 Level Questionnaire
ESR: Erythrocyte sedimentation rate
ET: Early termination
FSH: Follicle stimulating hormone
HbA1c: Hemoglobin A1c
HCRU: Healthcare Resource Utilization
Hs-CRP: High-sensitivity C-reactive Protein
JR: Joint replacement
K-L: Kellgren-Lawrence
MRI: Magnetic resonance imaging
NRS: Numeric Rating Scale (for walking index joint pain)
PGA: Patient Global Assessment
PK: Pharmacokinetic
Pre-Op: Pre-Operative
Pre-rand: Pre-randomization
SC: Subcutaneous
SF-36: 36-item Short Form Medical Outcomes Study Questionnaire Version 2
TSQM: Treatment Satisfaction Questionnaire for Medication
Visit: V
Week: Wk
WOCBP: Women of child-bearing potential
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index
WPAI-OA: Work Productivity and Activity Impairment-Osteoarthritis

Footnotes for Table 2 - the Schedule of Events

1. Patients who discontinue study medication before week 24 will be encouraged to follow the visit schedule through the remainder of the study. If a patient chooses to end study participation, he or she will be asked to return to the clinic as soon as possible for an early termination 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

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. Subcutaneous study drug administration will be the last procedure at each dosing visit, and will be done after all laboratory, PK, ADA and research samples have been collected and all study assessments 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 24.
7. Patients will complete the WOMAC pain subscale for both hips and knees at the screening visit. Then, the WOMAC Full Survey will be completed only for the index joint at subsequent visits.
8. Walking index joint pain NRS score will be recorded by the patient each day using their diary, starting during the pre-randomization period through week 24. Walking index joint pain NRS score will be recorded by the patient at the site at the week 24 visit.
9. If the pulse is less than 45 bpm, an ECG with rhythm strip will be obtained to confirm the heart rate and rhythm.
10. Blood pressure measurements to assess orthostatic hypotension may be discontinued following regulatory approval if the safety database does not reveal an imbalance for the fasinumab treated patients.
11. 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.
12. Imaging (X-ray and possibly 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. In the event that a patient must undergo joint arthroplasty during the study, the patient will complete the pre-operative JR study visit and the procedures outlined in the schedule of events for joint arthroplasty follow-up. The pre-operative questionnaire would be the Knee Society for knee replacements and the Harris Hip Score questionnaire for hip replacements. The pre-operative visit should be completed before joint arthroplasty if at all possible. Pre-operative imaging will be performed and submitted to the adjudication committee.
14. The purpose of this phone contact is to ask the patient if they have had or are scheduled (or on a waiting list) to have a JR. Pre-operative images will be submitted to the central reader for adjudication, if available
15. If the affected joint has undergone JR an X-ray may be substituted for an MRI
16. Samples will be analyzed by the central laboratory and results evaluated by the investigator
17. Only to be performed if postmenopausal status has to be assessed for female patients who are ≤59 years of age.
18. In the event of a positive urine pregnancy test result, the patient should have a serum pregnancy test with a negative result in order to continue study participation. If the serum pregnancy test is positive, the patient should be withdrawn from study drug and should be asked to return to the clinic for all remaining study visits per the visit schedule.
19. Collection of samples for PK, ADA, high sensitivity C-reactive protein (hs-CRP) and research are mandatory at the time points specified above. In addition, PK, ADA, hs-CRP 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 SC study drug administration on SC study drug dosing days
20. Research samples should be collected after the patients have been fasting overnight or for 8 hours (in the event of an afternoon visit).

Table 3: Follow-up Period for Patients Undergoing Joint Replacement Surgery on Study

Follow-up Study Day (Visit Window)[1]	**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 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 3 - 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.

10.3. Criteria for Potentially Clinically Significant Values (PCSV)

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

Parameter	PCSV	Comments
ALT/AST and Total Bilirubin	(ALT >3 ULN and TBILI>2 ULN) and baseline (ALT <=3 ULN or TBILI <=2 ULN) (AST >3 ULN and TBILI>2 ULN) and baseline (AST <=3 ULN or TBILI <=2 ULN) (ALT >3 ULN and TBILI>1.5 ULN) and baseline (ALT <=3 ULN or TBILI <=1.5 ULN) (AST >3 ULN and TBILI>1.5 ULN) and baseline (AST <=3 ULN or TBILI <=1.5 ULN)	FDA DILI Guidance July 2009.
ALT/AST and Total Bilirubin and ALP	(ALT >3 ULN and TBILI>2 ULN and ALP < 2 ULN) and baseline (ALT <=3 ULN or TBILI <=2 ULN or ALP >=2 ULN) (AST>3 ULN and TBILI>2 ULN and ALP < 2 ULN) and baseline (AST <=3 ULN or TBILI <=2 ULN or ALP >=2 ULN)	FDA DILI Guidance July 2009.
CPK*	>3 and ≤ 10 ULN and baseline ≤ 3ULN* >10 ULN and baseline ≤ 10ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. * At least one level is required; multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤3, >3 to ≤10, and > 10 category for baseline vs. post baseline may be provided
Creatinine	≥150 µmol/L (Adults) and baseline < 150 µmol/L >=30% change from baseline and <100% change from baseline ≥100% change from baseline	Benichou C., 1994 3 independent criteria
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L and <=408 µmol/L at baseline <120 µmol/L and >= 120 µmol/L at baseline	Harrison - Principles of internal Medicine 17th Ed., 2008. Two independent criteria
Blood Urea Nitrogen	≥17 mmol/L and <17 mmol/L at baseline	Two independent criteria

Parameter	PCSV	Comments
Chloride Hypochloraemia Hyperchloremia	 <80 mmol/L and baseline ≥ 80 mmol/L >115 mmol/L and baseline ≤ 115 mmol/L	Two independent criteria
Sodium Hyponatremia Hypernatremia	 ≤129 mmol/L and baseline > 129 mmol/L ≥160 mmol/L and baseline <160 mmol/L	Two independent criteria
Potassium Hypokalaemia Hyperkalaemia	 <3 mmol/L and baseline ≥ 3 mmol/L ≥5.5 mmol/L and baseline <5.5 mmol/L	FDA Feb 2005. Two independent criteria
Total Cholesterol	≥7.74 mmol/L and < 7.74 mmol/L at baseline	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L and < 4.6 mmol/L at baseline	Threshold for therapeutic intervention.
Glucose Hypoglycaemia Hyperglycaemia	 (≤3.9 mmol/L and <LLN) and (>3.9 mmol/L or >=LLN) at baseline ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted) and < 11.1 mmol/L (unfasted); <7 mmol/L (fasted) at baseline	 ADA May 2005. ADA Jan 2008.
HbA1c	>8% and <= 8% at baseline	HbA1c
Albumin	≤25 g/L and >25 g/L at baseline	Albumin
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	

Parameter	PCSV	Comments
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.
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.
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

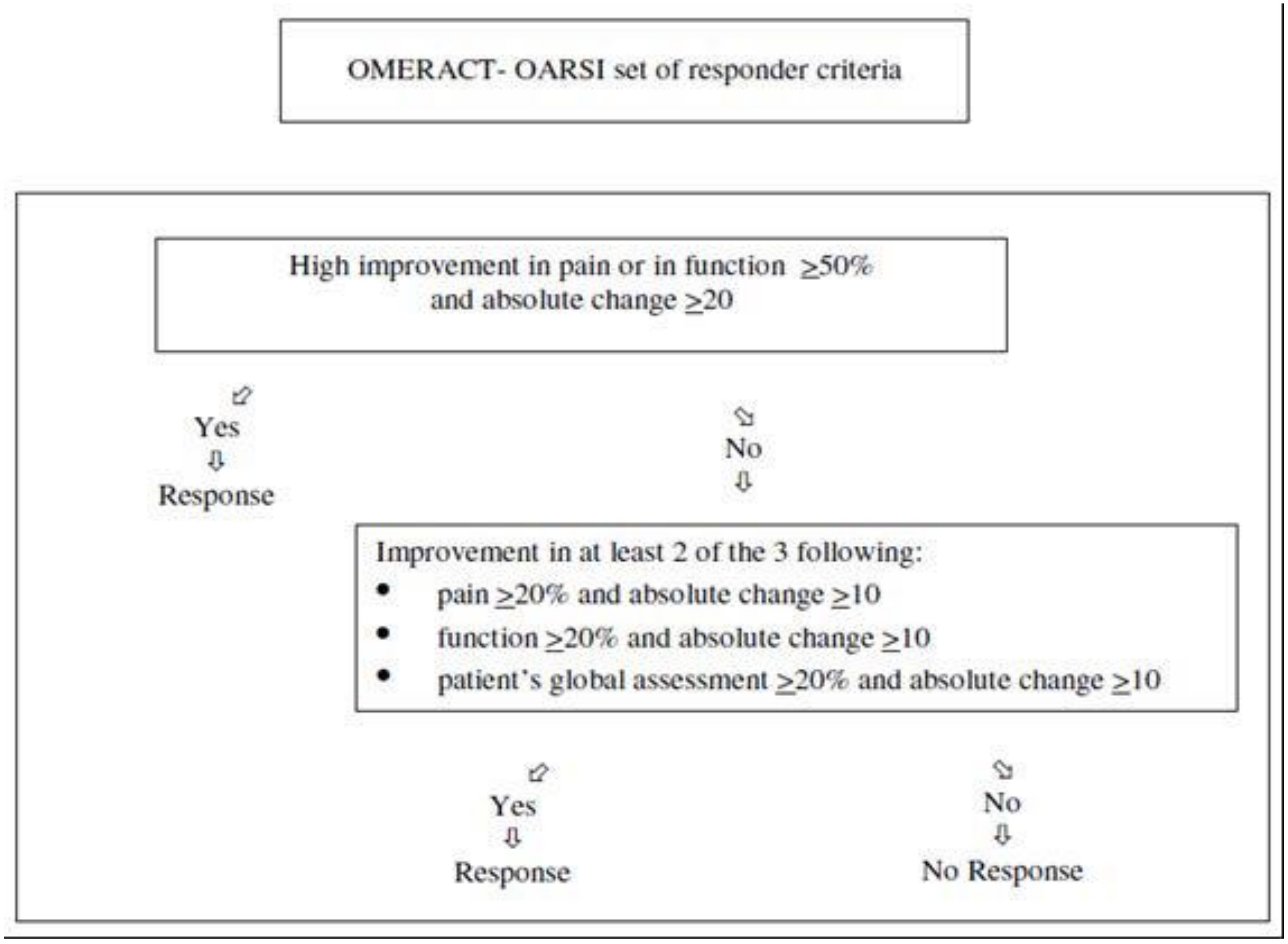
Parameter	PCSV	Comments
Vital Signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension	Su SBP < 160 mmHg - SBP St – Su ≤ - 20 mmHg DBP St – Su ≤ - 10 mmHg Su SBP ≥ 160 mmHg - SBP St – Su ≤ - 30 mmHg DBP St – Su ≤ - 15 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.
ECG parameters		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	PCSV	Comments
QTc	Absolute values (ms) >450 ms and baseline <=450 ms >480 ms and baseline <=480 ms >500 ms and <= 500 ms at baseline Increase from baseline Increase from baseline 30-60 ms Increase from baseline >60 ms	To be applied to any kind of QT correction formula. ΔQTc>60 ms are the PCSA to be identified in individual subjects/patients listings.

10.4. Protocol Deviations Excluding Patients from the PPS

PDID	Description of Protocol Deviation
1.05, 1.06, 1.08	Inclusion Criteria 4, 5, and 7 not met but subject randomized
2.11	Exclusion Criteria 10 met but subject randomized
3.02	Baseline visit not performed
3.16	Screening visit was not performed
5.14	WOMAC patient assessment was not administered at Week 24 Primary Endpoint Analysis
8.04	Rescue medication administered during a protocol-prohibited period prior to scheduled visit during treatment period
8.05	Use of opioid medications anytime during treatment period
8.06	Use of non-protocol specified NSAIDs any time during the treatment
F.02	Confirmed treatment unblinding (in error)

10.5. OMERACT – OARSI RESPONDER CRITERIA



Note that the criteria in the diagram above are based on standardized scores 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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